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(54) Title: USE OF MALARIA PARASITE ANION CHANNEL BLOCKERS FOR TREATING MALARIA

(57) Abstract: The present invention relates to the use of malaria anion channel blockers for treating malaria, a method for screening the activity of a compound in the above use, a method for diagnosing the severity of malaria disease of a subject, and novel compounds active as anion channel blockers.

USE OF MALARIA PARASITE ANION CHANNEL BLOCKERS FOR TREATING MALARIA

The present invention relates to the use of malaria anion channel blockers for treating malaria, a method for screening the activity a compound in the above use, a method for diagnosing the severity of malaria disease of a subject, and novel compounds active as anion channel blockers.

BACKGROUND ART

Malaria is a serious, acute and chronic relapsing infection characterised by periodic attacks of chills and fever, anaemia, enlargement of the spleen, and often fatal complications. Four species of parasites belonging to the genus *Plasmodium* is known to cause malaria. The most common of these malarial types, is *falciparum*, which causes the most severe symptoms and is the most frequently fatal. The parasites are transmitted to humans by the bite of mosquitoes. In the human being, the parasite enters an erythrocyte where it goes through various stages and divisions causing the erythrocyte to rupture, releasing the parasites into the bloodstream. The parasites can then infect other erythrocytes and the cycle of development is repeated.

Quinine has been used for centuries to alleviate malarial fevers, and newer synthetic drugs, such as chloroquine, can destroy the malarial parasites while they are living inside the erythrocytes. Now, however, most falciparum strains have become resistant against these synthetic drugs, and the incidence of malaria is increasing.

Thus, there is a continued strong interest in the development of a more selective and effective therapy with fewer side effects for the treatment of patients with malaria.

A voltage-dependent anion channel involved in the growth of the human malaria parasite in red blood cells is described in Nature, 31 August 2000; 406:1001-1005 ("A voltage-dependent channel involved in nutrient uptake by red blood cells infected with the malaria parasite", Desai, S. A., Bezrukov, S. M. and Zimmerberg, J.)

SUMMARY OF THE INVENTION

According to the invention it has now been found that malaria parasite anion channel blockers can be used for the treatment of malaria.

Thus, in its first aspect, the invention relates to the use of a malaria parasite anion channel blocker or a pharmaceutically acceptable salt or a prodrug thereof for the treatment, prevention or alleviation of malaria in a subject.

In its second aspect, the invention relates to the use of a specific malaria parasite anion channel blocker or a pharmaceutically acceptable salt or a prodrug

thereof for the manufacture of a medicament for the treatment, prevention or alleviation of malaria in a subject.

In its third aspect, the invention relates to the use of a compound of the general formula I

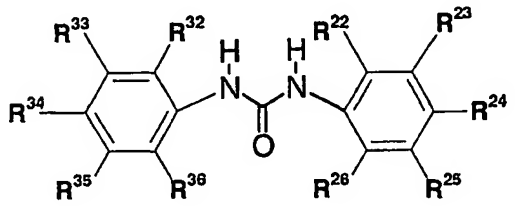
$$A\text{-}(X)_p\text{-}(Y)_q\text{-}(Z)_r\text{-}B \quad (I)$$

or a pharmaceutically acceptable salt or a prodrug thereof for the manufacture of a medicament for the treatment, prevention or alleviation of malaria in a subject.

In its fourth aspect, the invention relates to a method for screening a chemical compound for activity in the treatment, prevention or alleviation of malaria in a subject.

In its fifth aspect, the invention relates to a method for diagnosing the severity of malaria disease of a subject.

In its sixth aspect, the invention relates to a novel compound of the general formula II



II

Other objects of the invention will be apparent to the person skilled in the art from the following detailed description and examples.

DETAILED DISCLOSURE OF THE INVENTION

In its first aspect, the invention provides the use of a malaria parasite anion channel blocker or a pharmaceutically acceptable salt or a prodrug thereof for the manufacture of a medicament for the treatment, prevention or alleviation of malaria in a subject.

In a further aspect, the invention provides the use of a specific malaria parasite anion channel blocker or a pharmaceutically acceptable salt or a prodrug thereof for the manufacture of a medicament for the treatment, prevention or alleviation of malaria in a subject.

In a still further aspect, the invention provides a method for the treatment, prevention, or alleviation of malaria in a subject comprising administering to said subject a therapeutically effective amount of a malaria parasite anion channel blocker or a pharmaceutically acceptable salt or a prodrug thereof.

In a further aspect, the invention provides a method for the treatment, prevention, or alleviation of malaria in a subject comprising administering to said

subject a therapeutically effective amount of a specific malaria parasite anion channel blocker or a pharmaceutically acceptable salt or a prodrug thereof.

In the context of this invention, a malaria parasite anion channel is the anion channel of the malaria parasite *Plasmodium falciparum* as described in *Nature*, 31 August 2000; 406:1001-1005, or the equivalent anion channel of any other malaria parasite belonging to the genus *Plasmodium*.

In the context of this invention, an endogenous erythrocyte chloride channel is the chloride channel naturally present in erythrocytes of humans not infected by malaria.

In the context of this invention, a malaria parasite anion channel blocker is a compound that blocks the malaria parasite anion channel.

In the context of this invention, a specific malaria parasite anion channel blocker is a compound that blocks the malaria parasite anion channel without blocking the endogenous erythrocyte chloride channels.

The ability of a compound to block the malaria parasite anion channel can be measured as described in the method of Example 2.

The ability of a compound to block the endegenous erythrocyte chloride channel can be measured as described in the method of Example 1.

In one embodiment the ability of the malaria parasite anion channel blocker to block the malaria parasite anion channel show an IC_{50} value less than 100µM, preferably less than 10µM, and more preferably less than 1µM.

In a further embodiment the ability of the specific malaria parasite anion channel blocker to block the endogenous erythrocyte chloride channel show an IC_{50} value higher than 1µM, preferably higher than 10µM, and more preferably higher than 100µM.

In a further embodiment the malaria parasite anion channel blocker is a compound of general formula I.

In a further aspect, the invention provides the use of a compound of the general formula I

$$A\text{-}(X)_p\text{-}(Y)_q\text{-}(Z)_r\text{-}B \quad (I)$$

wherein

A represents a first ring structure selected from aryl, or heteroaryl;

which first ring structure is optionally substituted with one or more substituents independently selected from the group consisting of:

halogen, hydroxy, amino, oxy, cyano, nitro, trifluoromethyl, trifluoromethoxy, trifluorothiomethoxy,

alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, alkoxy,

aryl, arylalkyl, aryloxy, arylcarboxy, heteroaryl, -N(R^2)-aryl,

a 5- or 6-membered monocyclic heterocyclic group,

$-CO_2R^1$, $-COR^1$, -alkyl-CO_2R^1, -alkyl-COR^1,
$-N(R^2)_2$, -alkyl-$N(R^2)_2$, $-CO_2N(R^1)_2$, $-NHCOR^1$, $-CON(R^1)_2$, $-NHSO_2R^1$,
$-CONHSO_2R^1$, $-SO_2N(R^1)_2$, and $-SO_2OR^1$;
wherein each of the alkyl, alkoxy, and cycloalkyl is optionally substituted with one or more substitutents independently selected from the group consisting of:
halogen, hydroxy, amino, cyano, nitro, trifluoromethyl, trifluoromethoxy, trifluorothiomethoxy alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, and alkynyl;
each of the aryl, heteroaryl, and 5- or 6-membered monocyclic heterocyclic group is optionally substituted with one or more one or more substitutents independently selected from the group consisting of:
halogen, hydroxy, amino, cyano, nitro, trifluoromethyl, trifluoromethoxy, trifluorothiomethoxy alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, alkoxy,
aryl, heteroaryl, $-CO_2R^3$, $-COR^3$,
$-N(R^4)_2$, -alkyl-$N(R^4)_2$, $-CON(R^3)_2$, $-NHCOR^3$, $-CON(R^3)_2$, $-NHSO_2R^3$,
$-SO_2N(R^3)_2$, and $-SO_2OR^3$;
each of R^1 and R^3 independently is selected from the group consisting of:
hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroaryl, and a 5-8 membered ring optionally containing double bonds and optionally containing one or two heteroatoms, which heteroatoms can be substituted with alkyl or acyl;
or $(R^1)_2$ or $(R^3)_2$ independently together with the heteroatom to which it is connected represents a 5-8 membered ring optionally containing double bonds and optionally containing another heteroatom, which heteroatom can be substituted with alkyl or acyl;
each of R^2 and R^4 independently is hydrogen or alkyl;

B represents a second ring structure selected from aryl, or heteroaryl;
which second ring structure is substituted with one or more acidic functional group having a pKa value below 8, or a group which is convertible in vivo to such a group, or a bioisostere thereof;
and which second ring structure is furthermore optionally substituted with one or more substituents independently selected from the group consisting of:
halogen, hydroxy, amino, oxy, cyano, nitro, trifluoromethyl, trifluoromethoxy, trifluorothiomethoxy
alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, alkoxy,
aryl, arylalkyl, aryloxy, arylcarboxy, heteroaryl, $-N(R^6)$-aryl,
a 5- or 6-membered monocyclic heterocyclic group,
$-CO_2R^5$, $-COR^5$, -alkyl-CO_2R^5, -alkyl-COR^5,

$-N(R^6)_2$, -alkyl-$N(R^6)_2$, $-CON(R^5)_2$, $-NHCOR^5$, $-CON(R^5)_2$, $-NHSO_2R^5$, $-CONHSO_2R^5$, $-SO_2N(R^5)_2$, and $-SO_2OR^5$;

wherein each of the alkyl, alkoxy, and cycloalkyl is optionally substituted with one or more substitutents independently selected from the group consisting of:

halogen, hydroxy, amino, cyano, nitro, trifluoromethyl, trifluoromethoxy, trifluorothiomethoxy alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, and alkynyl;

each of the aryl, heteroaryl, and 5- or 6-membered monocyclic heterocyclic group is optionally substituted with one or more one or more substitutents independently selected from the group consisting of:

halogen, hydroxy, amino, cyano, nitro, trifluoromethyl, trifluoromethoxy, trifluorothiomethoxy alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, alkoxy,

aryl, heteroaryl, $-CO_2R^7$, $-COR^7$,

$-N(R^8)_2$, -alkyl-$N(R^8)_2$, $-CO_2N(R^7)_2$, $-NHCOR^7$, $-CON(R^7)_2$, $-NHSO_2R^7$, $-SO_2N(R^7)_2$, and $-SO_2OR^7$;

each of R^5 and R^7 independently is selected from the group consisting of:

hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroaryl, and

a 5-8 membered ring optionally containing double bonds and optionally containing one or two heteroatoms, which heteroatoms can be substituted by alkyl or acyl;

or $(R^5)_2$ or $(R^7)_2$ independently together with the heteroatom to which it is connected represents a 5-8 membered ring optionally containing double bonds and optionally containing another heteroatom, which heteroatom can be substituted by alkyl or acyl;

each of R^6 and R^8 independently is hydrogen or alkyl;

X, Y, and Z are independently selected from the group consisting of:

$-CO-$, $-CS-$, $-SO_2-$, $-C(=NR^9)-$, $-NR^{10}-$, $-(CH_2)_s-$, $-O-$, $-CH_2-NH-$, $-SO_2-NH-$, $-CH=CH-$, $-C\equiv C-$, and $-N=CH-$;

wherein s is 1, 2, or 3;

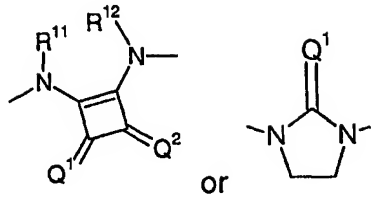
R^9 is hydrogen, alkyl, or cyano;

R^{10} is hydrogen or alkyl;

p, q, and r independently are 0 or 1;

the sum p+q+r is 1, 2, or 3;

or $-(X)_p-(Y)_q-(Z)_r-$ represents



wherein

Q^1 and Q^2 independently represent O or S;

R^{11} and R^{12} independently are hydrogen or alkyl;

or a pharmaceutically acceptable salt or a prodrug thereof

for the manufacture of a medicament for the treatment, prevention or alleviation of malaria in a subject.

In one embodiment, the acidic functional group having a pKa below 8, or a group which is convertible in vivo to such a group is selected from the group consisting of:

-COOH, $-CH_2CO_2R^{13}$, $-CON(R^{13})_2$, tetrazolyl, methyltetrazolyl, 3-oxo-1,2-dihydro-1,2,4-triazolyl, 2-oxo-3H-1,3,4-oxadiazolyl, 3-oxo-1,2-dihydro-1,2,4-triazolyl, 4-hydro-1,2,4-triazolyl, $-NHSO_2R^{13}$, $-CO_2R^{13}$, $-CO_2N(R^{13})_2$, $-SO_2OR^{13}$, $-SO_2N(R^{13})_2$, -CONHOH, $-CONHNH_2$, $-CONHSO_2R^{13}$, $-CONHSO_2OR^{13}$, $-PO(OR^{13})_2$, and $-SO_2OR^{13}$;

wherein each of R^{13} independently is selected from the group consisting of:

hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, aryl, aralkyl, and heteroaryl;

or R^{13} comprises a 5-8 membered ring optionally containing double bonds and optionally containing one or two heteroatoms, which heteroatoms can be substituted by alkyl or acyl;

or $(R^{13})_2$ together with the heteroatom to which it is connected represents a 5-8 membered ring optionally containing double bonds and optionally containing another heteroatom, which heteroatoms can be substituted by alkyl or acyl.

In a second embodiment, the bioisostere of the acidic functional group is two neighbouring fluoro.

In a further embodiment, the second ring structure is substituted with an acidic functional group having a pKa below 8, or a group which is convertible in vivo to such a group, or a bioisostere thereof, in the position nearest or second nearest to the position attached to $-(X)_p-(Y)_q-(Z)_r-$.

In a further embodiment, the acidic functional group having a pKa below 8, or a group which is convertible in vivo to such a group is selected from the group consisting of:

-COOH, $-CH_2CO_2R^{13}$, $-CON(R^{13})_2$, tetrazolyl, methyltetrazolyl, $-NHSO_2R^{13}$, $-CO_2R^{13}$, $-CO_2N(R^{13})_2$, $-SO_2N(R^{13})_2$, $-CONHSO_2R^{13}$, $-PO(OR^{13})_2$, and $-SO_2OR^{13}$; wherein R^{13} is as defined above.

In a still further embodiment, the first ring structure is optionally substituted with one or more substituents independently selected from the group consisting of: trifluoromethyl, halogen, alkyl, alkoxy, nitro, $-COR^1$, -COOH, $-CH_2CO_2R^1$, $-CON(R^1)_2$, $-NHSO_2R^1$, $-NHCOR^1$, $-CO_2R^1$, $-CO_2N(R^1)_2$, $-SO_2N(R^1)_2$, $-CONHSO_2R^1$, $-SO_2OR^1$, and aryl;

wherein the aryl optionally is substituted with one or more substituents selected from the group:

$-NO_2$, $-NHCOR^3$, $-CO_2R^3$, $-CON(R^3)_2$, $-NHSO_2R^3$, and $-SO_2N(R^3)_2$;

wherein R^1 and R^3 are defined as above.

In a further embodiment, the second ring structure is substituted with one or more acidic functional group having a pKa value below 8, or a group which is convertible in vivo to such a group, or a bioisostere thereof;

and which second ring structure is furthermore optionally substituted with one or more substituents independently selected from the group consisting of: alkyl, nitro, amino, alkylamino, CO_2R^9, CF_3, alkyl, halogen, hydroxy, alkoxy, $-NHCOR^5$, $-N(R^5)_2$, $-CON(R^5)_2$, and aryl,

wherein the aryl is optionally substituted with one or more substituents independently selected from the group consisting of:

$-NO_2$, $-CON(R^7)_2$, $-NHCOR^7$, $-SO_2N(R^7)_2$, and $-CO_2R^7$;

wherein R^5 and R^7 are defined as above.

In a still further embodiment, X is $-NR^9-$, Y is -CO- or -CS-, Z is $-NR^{10}-$, p is 1, q is 1 and r is 1; wherein R^{10} is defined as above.

In a further embodiment, Y is -CO- or -CS-, Z is $-NR^{10}-$, p is 0, q is 1, and r is 1.

In a still further embodiment, X is $-CH_2-$, Y is $-CH_2-$, Z is $-NR^{10}-$, p is 1, q is 1 and r is 1.

In a further embodiment, X is $-NR^{10}-$, Y is $-SO_2-$, Z is $-NR^{10}-$, p is 1, q is 1 and r is 1.

In a still further embodiment, X is $-CH_2-NH-$, Y is -CO- or -CS-, Z is $-NR^{10}-$, p is 1, q is 1 and r is 1.

In a further embodiment, X is -O-, Y is -CO-, Z is -NR10-, p is 1, q is 1 and r is 1.

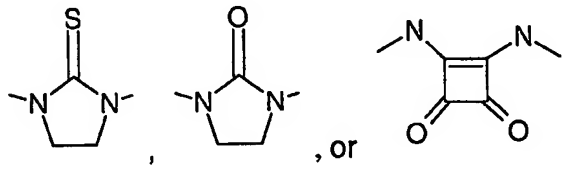
In a still further embodiment, X is $-SO_2-NH-$, Y is -CO-, Z is -NH-, p is 1, q is 1 and r is 1.

In a further embodiment, X is $-NR^{10}-$, Y is $-(CH_2)_s-$, Z is $-NR^{10}-$, p is 1, q is 1 and r is 1; wherein s is defined as above.

In a special embodiment, R^{10} is hydrogen.

In a further embodiment, s is 2.

In a still further embodiment, $-(X)_p-(Y)_q-(Z)_r-$ represents



In a further embodiment, the first ring structure is phenyl, naphthyl, indanyl, or pyridyl.

In a still further embodiment, the second ring structure is phenyl, naphthyl, indanyl or pyridyl.

In a special embodiment, the first ring structure is phenyl, the second ring structure is phenyl, and $-(X)_p-(Y)_q-(Z)_r-$ represents -NH-CO-NH-.

In a special embodiment, the compound of general formula I is selected from:

N-3-Trifluoromethylphenyl-*N'*-2-carboxyphenyl urea

N-3-Trifluoromethylphenyl-*N'*-3-carboxyphenyl urea;

N-(2-Methoxy-5-chlorophenyl)-*N'*-3-carboxyphenyl urea;

N-3-Trifluoromethylphenyl-*N'*-(2-carboxy-5-nitrophenyl) urea;

N-3-Trifluoromethylphenyl-*N'*-(2-carboxy-4-methylphenyl) urea;

N-3-Trifluoromethylphenyl-*N'*-(4-bromo-2-carboxyphenyl) urea;

N-3-Trifluoromethylphenyl-*N'*-3-carbamoylphenyl urea;

N-3-Trifluoromethylphenyl-*N'*-3-sulfamoylphenyl urea;

N-3-Trifluoromethylphenyl-*N'*-(5-chloro-2-phenylsulfonamidocarbonylphenyl) urea;

N-3-Trifluoromethylphenyl-*N'*-2-methylsulfonamidocarbonylphenyl urea;

N-3-Trifluoromethylphenyl-*N'*-(6-methyl-2-carboxyphenyl) urea;

N-3-Trifluoromethylphenyl-*N'*-(3-methyl-2-carboxyphenyl) urea;

N-3-Trifluoromethylphenyl-*N'*-(4-hydroxy-2-carboxyphenyl) urea;

N-4-Nitrophenyl-*N'*-2-carboxyphenyl urea;

N-3-Trifluoromethylphenyl-*N'*-2-carboxymethylphenyl urea;

N-3-Trifluoromethylphenyl-*N'*-2-sulfophenyl urea;

N-3-Trifluoromethylphenyl-*N'*-2-carboxyphenyl thiourea;

N-3-Trifluoromethylphenyl-*N'*-(2-carboxy-5-trifluoromethylphenyl) urea;

N-3-Trifluoromethylphenyl-*N'*-(4,5-dimethoxy-2-carboxyphenyl) urea;

N-3-carboxyphenyl-*N'*-(2-hydroxy-5-chlorophenyl) urea;

N-3-carbamoylphenyl-*N'*-(2-hydroxy-5-chlorophenyl) urea;

N-3-Trifluoromethylphenyl-*N'*-(2-hydroxy-4-nitro-5-carboxyphenyl) urea;

N-3-Trifluoromethylphenyl-*N'*-(4-carboxy-5-chloro-2-hydroxyphenyl) urea;

N-3-Trifluoromethylphenyl-*N'*-(2-amino-5-chlorophenyl) urea;

N-3-Trifluoromethylphenyl-*N'*-(5-chloro -2-methanesulfonylaminophenyl) urea;
N-3-Trifluoromethylphenyl-*N'*-2-carboxyphenyl urea isopropyl ester;
N-3-Trifluoromethylphenyl-*N'*-2-carboxyphenyl urea methyl ester;
N-3-Trifluoromethylphenyl-*N'*-2-hydrazinocarbonylphenyl urea;
N-3-Trifluoromethylphenyl-*N'*-2-hydroxylaminocarbonylphenyl urea;
2-(3'-Trifluoromethylbenzylcarboxamido)benzoic acid;
N-3-Trifluoromethylphenyl-*N'*-4-carboxyphenyl urea;
N-3-Trifluoromethylphenyl-*N'*-(2-carboxy-4-nitrophenyl) urea;
N-3-Trifluoromethylphenyl-*N'*-2-carboxynapht-3-yl urea;
N-3-Trifluoromethylphenyl-*N'*-(4-methoxy-2-carboxyphenyl) urea;
N-3-Methoxyphenyl-*N'*-2-carboxyphenyl urea;
N-4-Bromophenyl-*N'*-2-carboxyphenyl urea;
N-3-Nitrophenyl-*N'*-2-carboxyphenyl urea;
N-2-Methoxyphenyl-*N'*-2-carboxyphenyl urea;
N-4-Methoxyphenyl-*N'*-2-carboxyphenyl urea;
N-1-Naphthyl-*N'*-2-carboxyphenyl urea;
N-2-Trifluoromethylphenyl-*N'*-2-carboxyphenyl urea;
N-4-Methylphenylsulfonyl-*N'*-2-carboxyphenyl urea;
N-3-Trifluoromethylphenyl-*N'*-(2-ethyloxycarbonylphenyl)-1,2-diaminoethane;
N-3-Trifluoromethylphenyl-*N'*-2-carboxyphenyl sulfamide;
N-3-Trifluoromethylbenzyl-*N'*-2-carboxyphenyl urea;
N-3-(Trifluoromethyl-4-phenylphenyl)-*N'*-2-carboxyphenyl urea;
2-(3'-Trifluoromethylphenyloxycarbonylamino)benzoic acid;
N-3-Trifluoromethylphenyl-*N'*-(5-chloro-2-aminophenyl) urea;
N-3-Trifluoromethylphenyl-*N'*-(4-nitro-2-(1-*H*-tetrazol-5-yl)phenyl) urea;
N-3-Trifluoromethylphenyl-*N'*-[4-(2-naphthyl)-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-3-Trifluoromethylphenyl-*N'*-[4-(3-pyridyl)-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-3-Trifluoromethylphenyl-*N'*-[4-(1-naphthyl)-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-3-Trifluoromethylphenyl-*N'*-[4-(4-trifluoromethylphenyl)-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-3-Trifluoromethylphenyl-*N'*-[4-(3-furyl)-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-3-Trifluoromethylphenyl-*N'*-[4-(3-thienyl)-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-3-Trifluoromethylphenyl-*N'*-[4-(3-nitrophenyl)-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-3-Trifluoromethylphenyl-*N'*-[4-(4-ethoxycarbonylphenyl)-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-3-Trifluoromethylphenyl-*N'*-[4-(4-dimethylaminocarbonylphenyl)-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-3-Trifluoromethylphenyl-*N'*-[4-(4-aminocarbonylphenyl)-2-(1-*H*-tetrazol-5-yl)phenyl] urea;

N-3-Trifluoromethylphenyl-*N'*-2-(4-hydroxy-1,2,4-triazol-3-yl)phenyl urea;
N-3-Trifluoromethylphenyl-*N'*-2-(3-oxo-1,2-dihydro-1,2,4-triazol-1-yl)phenyl urea;
N-3-Trifluoromethylphenyl-*N'*-2-(2-oxo-3H-1,3,4-oxadiazol-5-yl)phenyl urea;
N-3-Trifluoromethylphenyl-*N'*-[5-phenyl-2-(3-oxo-1,2-dihydro-1,2,4-triazol-1-yl)phenyl] urea;
N-3-Trifluoromethylphenyl-*N'*-[4-amino-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-3-Trifluoromethylphenyl-*N'*-[4-acetylamino-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-3-Trifluoromethylphenyl-*N'*-[4-benzoylamino-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-3-Trifluoromethylphenyl-*N'*-[4-(4-carboxyphenyl)-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-3-Trifluoromethylphenyl-*N'*-[4-(4-anilinocarbonylphenyl)-2-(1-*H*-tetrazol-5-yl)]phenyl urea;
N-4-Biphenylyl-*N'*-2-(1-*H*-tetrazol-5-yl)phenyl urea;
N-3-Biphenylyl-*N'*-2-(1-*H*-tetrazol-5-yl)phenyl urea;
N-5-Indanyl-*N'*-2-(1-*H*-tetrazol-5-yl)phenyl urea;
N-3-Bromophenyl-*N'*-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-3-Acetylphenyl-*N'*-2-(1-*H*-tetrazol-5-yl)phenyl urea;
N-3-Biphenylyl-*N'*-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-3-(3-Pyridyl)phenyl-*N'*-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-3-Trifluoromethylphenyl-*N'*-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-3-Trifluoromethylphenyl-*N'*-[2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-3-Trifluoromethylphenyl-*N'*-2-(1-*H*-tetrazol-5-yl)phenyl thiourea;
N-3-Trifluoromethylphenyl-*N'*-[4-phenyl-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-4-Trifluoromethylphenyl-*N'*-2-(1-*H*-tetrazol-5-yl)phenyl urea;
N-3-Chlorophenyl-*N'*-2-(1-*H*-tetrazol-5-yl)phenyl urea;
N-Phenyl-*N'*-2-(1-*H*-tetrazol-5-yl)phenyl urea;
N-3-Bromophenyl-*N'*-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
3-[4-Bromo-2-(1-*H*-tetrazol-5-yl)-phenylamino]-4-(3-trifluoromethyl-phenylamino)-3-cyclobuten-1,2-dione;
3-(3-Bromo-phenylamino)-4-[4-bromo-(1-*H*-tetrazol-5-yl)-phenylamino]-3-cyclobuten-1,2-dione;
3-(3-Bromo-phenylamino)-4-[4´-(N,N-dimethyl sulfonamide)-2-(1-*H*-tetrazol-5-yl)-biphenylamino]-3-cyclobuten-1,2-dione;
3-(3-Bromo-phenylamino)-4-[2-(1-*H*-tetrazol-5-yl)-biphenylamino]-3-cyclobuten-1,2-dione;
N-Phenyl-*N*´-(2-carboxyphenyl) urea;
N-3-Trifluoromethylphenyl-*N*´-(2-carboxyphenyl)-*N*´-methyl urea;
N-3-Trifluoromethylphenyl-*N*´-(4-bromo-2-carboxyphenyl) urea;
N-3-Trifluoromethylphenyl-*N*´-(2-carboxy-4-chlorophenyl) urea;
N-3-Trifluoromethylphenyl-*N'*-(5-bromo-2-carboxyphenyl) urea;

N-3-Trifluoromethylphenyl-*N'*-(2-carboxy-5-chlorophenyl) urea;
N-3-Trifluoromethylphenyl-*N'*-(2-carboxy-4-fluorophenyl) urea;
N-3-Bromophenyl)-*N'*-[2-(1-*H*-tetrazol-5-yl)-4-biphenyl] urea;
N-3-Trifluoromethylphenyl)-*N'*-[4'-(N,N-dimethylsulfamoyl)-2-(1-*H*-tetrazol-5-yl)-4-biphenyl] urea;
N-3-Bromophenyl-*N'*-[4'-(N,N-dimethylsulfamoyl)-2-(1-*H*-tetrazol-5-yl)-4-biphenyl] urea;
N-3-Bromophenyl-*N'*-[4'-(N,N-dimethylcarbamoyl)-2-(1-*H*-tetrazol-5-yl)-4-biphenyl] urea;
N-3-Trifluromethylphenyl-*N'*-[4-amino-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-3-Trifluoromethylphenyl-*N'*-[4-acetylamino-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-3-Trifluoromethylphenyl-*N'*-[4'-carbamoyl-2-(1-*H*-tetrazol-5-yl)-4-biphenyl] urea;
N-3-Trifluoromethylphenyl-*N'*-[4'-(N,N-dimethylcarbamoyl)-2-(1-*H*-tetrazol-5-yl)-4-biphenyl] urea;
N-3-Trifluoromethylphenyl-*N'*-[4'-carboxy-2-(1-*H*-tetrazol-5-yl)-4-biphenyl] urea;
1-(3-Trifluoromethylphenyl)-3-(2-carboxyphenyl)-2-imidazolidone;
N-3-Trifluoromethylphenyl-*N'*-[4-(4-benzoylcarbonylphenyl)-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-4-Biphenylyl-*N'*-2-(1-*H*-tetrazol-5-yl)phenyl urea;
N-3-Bromophenyl-*N'*-[3'-nitro-2-(1-*H*-tetrazol-5-yl)biphenyl] urea;
N-3-Bromophenyl-*N'*-[4'-(sulfoamido-N-methylpiperazinium chloride)-2-(1-*H*-tetrazol-5-yl)-4-biphenyl] urea;
N-3-Bromophenyl-*N'*-[4'-(carbamoyl-N-methylpiperazine)-2-(1-*H*-tetrazol-5-yl)-4-biphenyl] urea;
N-3,5-Dichlorophenyl-*N'*-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-4-Trifluoromethylphenyl-*N'*-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-4-Bromophenyl-*N'*-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-3-Methoxyphenyl-*N'*-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-3-Chlorophenyl-*N'*-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-3-Methylphenyl-*N'*-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-3,4-Dichlorophenyl-*N'*-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-2-Naphthyl-*N'*-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-(4-Methyl-3-nitrophenyl)-*N'*-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-(2-Chloro-4-trifluoromethylphenyl)-*N'*-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-3,5-Di(trifluoromethyl)phenyl-*N'*-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-3,5-Dimethylphenyl-*N'*-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-4-Ethoxyophenyl-*N'*-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-4-Methoxyphenyl-*N'*-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-2-Trifluoromethylphenyl-*N'*-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea;

N-2-Bromophenyl-*N*´-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-2-Chlorophenyl-*N*´-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-2-Fluorophenyl-*N*´-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-(4-Chloro-3-trifluoromethylphenyl)-*N*´-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-3-Bromophenyl-*N*´-2,3-difluorophenyl urea;
N-2-Methylphenyl-*N*´-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-2-Ethylphenyl-*N*´-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-4-Methylphenyl-*N*´-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-2-Nitrophenyl-*N*´-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-3-Fluorophenyl-*N*´-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-4-(2-Propyl)phenyl-*N*´-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-3-Nitrophenyl-*N*´-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-3-Acetylphenyl-*N*´-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-4-Nitrophenyl-*N*´-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-3-Trifluoromethylphenyl-*N*´-2-carboxyphenyl urea;
N-Phenyl-*N*´-2-carboxyphenyl urea;
N-3-Trifluoromethylphenyl-*N*´-2-carboxyphenyl-N-methyl urea;
N-3-Trifluoromethylphenyl-*N*´-[4´-(N-phenylcarbamoyl)-2-(1-*H*-tetrazol-5-yl)-4-biphenyl] urea;
N-(2-Indan)-*N*´-2-(1-*H*-tetrazol-5-yl)phenyl urea;
N-(4-Biphenyl)-*N*´-2-(1-*H*-tetrazol-5-yl)phenyl urea;
N-(3-Biphenyl)-*N*´-2-(1-*H*-tetrazol-5-yl)phenyl urea;
N-3-Acetylphenyl-*N*´-2-(1-*H*-tetrazol-5-yl)phenyl urea;
N-3-Trifluoromethylphenyl-*N*´-[2-(1-methyltetrazol-5-yl)-4-biphenyl] urea;
N-(3-Biphenyl)-*N*´-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-3-(3-Pyridyl)phenyl-*N*´-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea hydrochloride;
N-3-Bromophenyl-*N*´-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-(4-Biphenylyl)-*N*'-2-(1-*H*-tetrazol-5-yl)phenyl urea;
N-(3-biphenylyl)-*N*'-2-(1-*H*-tetrazol-5-yl)phenyl urea;
N-(5-Indanyl)-*N*'-2-(1-*H*-tetrazol-5-yl)phenyl urea; and
pharmaceutically acceptable salts and prodrugs thereof.

The above compounds and their preparation are described in WO97/45400, WO98/47879, WO00/20378, and WO00/24707.

In a further special embodiment, the compound of general formula I is selected from the following list of compounds (melting points of the compounds are given in brackets):
N-(2-Chloro-5-trifluoromethylphenyl)-*N*´-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea (MP. 269-271°C);

N-4-Bromophenyl-*N'*-(2-carboxy-5-chlorophenyl) urea (MP. 208-209°C);
N-4-Trifluoromethylphenyl-*N'*-(2-carboxy-5-chlorophenyl) urea (MP. 167.1-169.3°C);
N-3-Bromophenyl-*N'*-(2-carboxy-5-chlorophenyl) urea (MP. 210-213°C);
N-3-Nitrophenyl-*N'*-(2-carboxy-5-chlorophenyl) urea (MP. 209-212°C);
N-3-Methoxyphenyl-*N'*-(2-carboxy-5-chlorophenyl) urea (MP. 181.5-183.1°C);
N-(4-Chloro-3-trifluoromethylphenyl)-*N'*-(2-carboxy-5-chlorophenyl) urea (MP. 186.8-188°C);
N-3-Fluorophenyl-*N'*-(2-carboxy-5-chlorophenyl) urea (MP. 175.4-177.6°C);
N-3-Fluorophenyl-*N'*-(2-carboxy-5-fluorophenyl) urea (MP. 175.6-178.9°C);
N-3-Trifluoromethylphenyl-*N'*-(2-carboxy-4,5-difluorophenyl) urea (MP. 183.6-184.9°C);
N-3,5-Bis(trifluoromethyl)phenyl-*N'*-(2-carboxy-5-chlorophenyl) urea (MP. 203-205°C);
N-3-Trifluoromethylphenyl-*N'*-(2-carboxy-5-nitrophenyl) urea (MP. 192.1-193.5°C);
N-3,4-Dichlorophenyl-*N'*-[5-methyl-2-(1-*H*-tetrazol-5-yl)phenyl] urea (MP. 185-185.4°C);
N-3,4-Dichlorophenyl-*N'*-[5-chloro-2-(1-*H*-tetrazol-5-yl)phenyl] urea (MP. 250.1-251°C);
N-3-Trifluoromethylphenyl-*N'*-(3-carboxy-4-chlorophenyl) urea;
N-(3-Chloro-4-hydroxyphenyl)-*N'*-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea (MP. 187.8-192°C);
N-2,3,4-Trifluorophenyl-*N'*-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea (MP. 265.3°C);
N-3,4-Difluorophenyl-*N'*-[4-bromo-2-(1-*H*-tetrazol-5yl)phenyl] urea (MP. 270.2°C);
N-3-Chlorophenyl-*N'*-2,3-difluorophenyl urea (MP. 176-177°C);
N-(3-Chloro-4-fluorophenyl)-*N'*-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea (MP. 256-258°C);
N-2,4,5-Trifluorophenyl-*N'*-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea (MP. 272-273°C);
N-3,5-Bis(trifluoromethyl)phenyl-*N'*-[2-(1-*H*-tetrazol-5-yl)phenyl] urea (MP. 225-227°C);
N-3,5-Bis(trifluoromethyl)phenyl-*N'*-[2,4-dibromo-6-(1-*H*-tetrazol-5-yl)phenyl] urea (MP. 216.1-218°C);
N-(4-Fluoro-3-trifluoromethylphenyl)-*N'*-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea (MP. 259-260°C);
N-3,5-Difluorophenyl-*N'*-[4-bromo-2-(1-*H*-tetrazol-5-yl)-phenyl] urea (MP. 264.2°C);
N-3,5-Bis(trifluoromethyl)phenyl-*N'*-[4'-(*N*,*N*-dimethylsulfamoyl)-2-(1-*H*-tetrazol-5-yl)-4-biphenyl] urea (MP. 255.6-257.7°C);
N-3,5-Dichlorophenyl-*N'*-[4'-(*N*,*N*-dimethylsulfamoyl)-2-(1-*H*-tetrazol-5-yl)-4-biphenyl] urea (MP. 234.3-234.6°C);
N-2,3-Difluorophenyl-*N'*-3-trifluoromethylphenyl urea (MP. 166.1-167.7°C);
N-2,3-Difluorophenyl-*N'*-(4-chloro-3-trifluoromethylphenyl) urea (MP. 183.8-184.9°C);
N-3,4-Dichlorophenyl-*N'*-2,3-difluorophenyl urea (MP. 216-218°C);

N-2,3-Difluorophenyl-*N'*-3-trifluoromethylphenyl thiourea (MP. 88.6-90.4°C);
N-2,3-Difluorophenyl-*N'*-2-fluorophenyl urea (MP. 209-210°C);
N-2,3-Difluorophenyl-*N'*-3-methoxyphenyl urea (MP. 174.5-176.1°C);
N-3,4-Dichlorophenyl-*N'*-2,3,4-trifluorophenyl urea (MP. 242.7-247.8°C);
N-(4-Chloro-3-trifluoromethylphenyl)-*N'*-2,3,4-trifluorophenyl urea (MP. 198.9-200°C);
N-3-Chlorophenyl-*N'*-(2-hydroxy-4-methylphenyl) urea (MP. 196.2°C);
N-2,3-Difluorophenyl-*N'*-[3-(pyridin-3-yl)-phenyl] urea (MP. 178.7-179.8°C);
N-3,5-Dichlorophenyl-*N'*-2,3-difluorophenyl urea (MP. 212-215°C);
N-2,3-Difluorophenyl-*N'*-3-nitrophenyl urea (MP. 210-211°C); and
pharmaceutically acceptable salts and prodrugs thereof.

The above compounds are prepared according to the methods as described in WO97/45400, WO98/47879, WO00/20378, WO00/24707, and in Examples 4 and 5.

In a further aspect, the invention provides a method of treatment, prevention or alleviation of malaria in a subject, which method comprises administering to said subject a therapeutically effective amount of a compound of general formula I or a pharmaceutically acceptable salt or a prodrug thereof.

In a still further aspect, the invention provides a method for screening a chemical compound for activity in the treatment, prevention or alleviation of malaria in a subject, which method comprises the following steps:

- subjecting a malaria anion channel containing cell to the action of the chemical compound;
- monitoring the membrane potential, and the conductive netflux of chloride of the malaria anion channel containing cell; and
- calculating the ability of the compound to block the malaria anion channel.

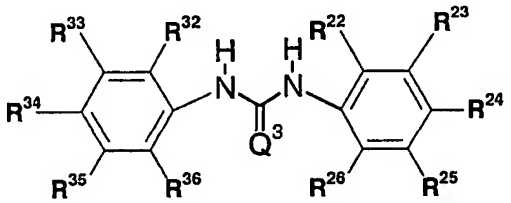
In one embodiment, the above method furthermore comprises the following steps:

- subjecting an erythrocyte chloride channel containing cell to the action of the chemical compound;
- monitoring the membrane potential, and the conductive netflux of chloride of the erythrocyte chloride channel containing cell
- calculating the ability of the compound to block the erythrocyte chloride channel containing cell.

In a further aspect, the invention provides a method for diagnosing the severity of malaria disease of a subject, which method comprises the following steps:

- isolating erythrocytes of a blood sample of said subject;
- blocking the endogenous erythrocyte chloride channels of the erythrocytes;
- monitoring the membrane potential, and the conductive netflux of chloride over the erythrocyte cell membranes;
- calculating the residual chloride conductance of the erythrocyte cell membranes;
- calculating the degree of parasitamia.

In a still further aspect, the invention provides a novel compound of the general formula II



II

wherein one of R^{22}, R^{23}, R^{24}, R^{25}, or R^{26} is
-COOH, -OH, or 1-H-tetrazol-5-yl; or R^{22} and R^{23} are fluoro;
or R^{23} and R^{24} are fluoro;
the other three or four of R^{22}, R^{23}, R^{24}, R^{25}, and R^{26} are independently selected from the group consisting of:
hydrogen, chloro, fluoro, nitro, methyl, bromo, and 4-(dimethylsulfamoyl)-phenyl;
R^{32}, R^{33}, R^{34}, R^{35}, and R^{36} are independently selected from the group consisting of:
hydrogen, bromo, trifluoromethyl, nitro, methoxy, chloro, fluoro, and hydroxy;
Q^3 is O or S;
or a pharmaceutically acceptable salt or a prodrug thereof.

In one embodiment of the compound of formula II, R^{22} is 1-H-tetrazol-5-yl. In a second embodiment, R^{22} is –COOH. In a third embodiment, R^{22} is –OH. In a further embodiment, R^{22} and R^{23} are fluoro. In a still further embodiment, R^{23} and R^{24} are fluoro. In a further embodiment Q^3 is O. In a still further embodiment, Q^3 is S.

In a special embodiment, the compound of formula II is selected from
N-(2-Chloro-5-trifluoromethylphenyl)-N´-[4-bromo-2-(1-H-tetrazol-5-yl)phenyl] urea;
N-4-Bromophenyl-*N*´-(2-carboxy-5-chlorophenyl) urea;
N-4-Trifluoromethylphenyl-*N*´-(2-carboxy-5-chlorophenyl) urea;
N-3-Bromophenyl-*N*´-(2-carboxy-5-chlorophenyl) urea;
N-3-nitrophenyl-*N*´-(2-carboxy-5-chlorophenyl) urea;
N-3-Methoxyphenyl-*N*´-(2-carboxy-5-chlorophenyl) urea;
N-(4-Chloro-3-trifluoromethylphenyl)-*N*´-(2-carboxy-5-chlorophenyl) urea;
N-3-Fluorophenyl-*N*´-(2-carboxy-5-chlorophenyl) urea;

N-3-fluorophenyl-*N'*-(2-carboxy-5-fluorophenyl) urea;
N-3-Trifluoromethylphenyl-*N'*-(2-carboxy-4,5-difluorophenyl) urea;
N-3,5-Bis(trifluoromethyl)phenyl-*N'*-(2-carboxy-5-chlorophenyl) urea;
N-3-Trifluoromethylphenyl-*N'*-(2-carboxy-5-nitrophenyl) urea;
N-3,4-Dichlorophenyl-*N'*-[5-methyl-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-3,4-Dichlorophenyl-*N'*-[5-chloro-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-3-Trifluoromethylpheny)-*N'*-(3-carboxy-4-chlorophenyl) urea;
N-(3-Chloro-4-hydroxyphenyl)-*N'*-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-2,3,4-Trifluorophenyl-*N'*-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-3,4-Difluorophenyl-*N'*-[4-bromo-2-(1-*H*-tetrazol-5yl)phenyl] urea;
N-3-Chlorophenyl-*N'*-2,3-difluorophenyl urea;
N-(3-Chloro-4-fluorophenyl)-*N'*-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-2,4,5-Trifluorophenyl-*N'*-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl) urea;
N-3,5-Bis(trifluoromethyl)phenyl-*N'*-[2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-3,5-Bis(trifluoromethyl)phenyl-*N'*-[2,4-dibromo-6-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-(4-Fluoro-3-trifluoromethylphenyl)-*N'*-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-3,5-Difluorophenyl-*N'*-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-3,5-Bis(trifluoromethyl)phenyl)-*N'*-[4'-(*N*,*N*-dimethylsulfamoyl)-2-(1-*H*-tetrazol-5-yl)-4-biphenyl] urea;
N-3,5-Dichlorophenyl-*N'*-[4'-(*N*,*N*-dimethylsulfamoyl)-2-(1-*H*-tetrazol-5-yl)-4-biphenyl] urea;
N-2,3-Difluorophenyl-*N'*-3-trifluoromethylphenyl urea;
N-2,3-Difluorophenyl-*N'*-(4-chloro-3-trifluoromethylphenyl) urea;
N-3,4-Dichlorophenyl-*N'*-2,3-difluorophenyl;
N-2,3-Difluorophenyl-*N'*-3-trifluoromethylphenyl thiourea;
N-2,3-Difluorophenyl-*N'*-2-fluorophenyl urea;
N-2,3-Difluorophenyl-*N'*-3-methoxyphenyl urea;
N-3,4-Dichlorophenyl-*N'*-2,3,4-trifluorophenyl urea;
N-(4-Chloro-3-trifluoromethylphenyl)-*N'*-2,3,4-trifluorophenyl urea;
N-3-Chlorophenyl-*N'*-(2-hydroxy-4-methylphenyl) urea;
N-2,3-Difluorophenyl-*N'*-[3-(pyridin-3-yl)phenyl] urea;
N-3-Chlorophenyl-*N'*-2,3-difluorophenyl urea;
N-3,5-Dichlorophenyl-*N'*-2,3-difluorophenyl urea;
N-2,3-Difluorophenyl-*N'*-3-nitrophenyl urea; and
pharmaceutically acceptable salts and prodrugs thereof.

Besides being active as malaria parasite anion channel blockers, the compounds of general formula II are blockers of chloride channels and thereby useful for the treatment of sickle-cell anaemia, brain oedema following ischaemia or tumours, diarrhea, hypertension (diuretic), bone metabolic disorders, osteoclast associated

disorders, bone metastasizing cancers, glaucoma, allergic or inflammatory conditions or for healing ulcers.

Any possible combination of two or more of the embodiments described herein is comprised within the scope of the present invention.

Definition of Substituents

In the context of this invention halogen represents a fluorine, a chlorine, a bromine or an iodine atom.

Alkyl means a straight chain or branched chain of one to six carbon atoms, including but not limited to, methyl, ethyl, propyl, isopropyl, butyl, isobutyl, t-butyl, pentyl, and hexyl; methyl, ethyl, propyl and isopropyl are preferred groups.

Alkoxy is O-alkyl, wherein alkyl is as defined above.

Acyl is -CO-alkyl wherein alkyl is as defined above.

Aryl is a carbocyclic aromatic ring system such as phenyl, naphthyl (1-naphthyl or 2-naphthyl), indanyl, and indenyl.

The acidic functional group having a pKa below 8 or a group which is converted in vivo to such group are groups such as 3-hydroxy-4-oxo-pyranyl, 2-hydroxy-4-oxo-pyrimidyl, 3,5-dioxo-1,2,4-oxadiazolidinyl, 2,4-dioxo-imidazolidinyl, 2,5-dioxo-3-hydroxy-pyrrolyl, 2,5-dioxo-pyrrolidinyl, 2,4-dioxo-1,3-thiazolidinyl, 3-hydroxy-isoxazolyl, 5-hydroxy-isoxazolyl, 3-hydroxy-isothiazolyl, 3-hydroxy-1,2,5-thiadiazolyl, tetrazolyl, 1-methyltetrazolyl, 3-hydroxy-triazolyl, 3-hydroxy-pyrazolyl, 2-hydroxy-1,3,4-oxadiazolyl, 3-oxo-1,2-dihydro-1,2,4-triazolyl, 2-oxo-3H-1,3,4-oxadiazolyl, 4-hydroxy-1,2,4-triazolyl, 2-hydroxy-1,3,4-oxadiazolyl or 2-hydroxy-3,4-dioxo-cyclobutenyl, NH_2, $-N(R^{13})_2$, $-OR^{13}$, $-CO_2R^{13}$, $-CH_2CO_2R^{13}$, $-CON(R^{13})_2$, $-NHSO_2R^{13}$, $-SO_2N(R^{13})_2$, $-SO_2OR^{13}$, $-SO_2R^{13}$, $-PO(OR^{13})_2$, $-PO_3H_2$, $-PO_3R^2H$, $-PO_2NH_2$, -CONHOH, -CONHCN, $-CONHSO_2R^{13}$, $-CONHSO_2OR^{13}$, and $-CONHNH_2$;

wherein each of R^{13} independently is selected from the group consisting of: hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, aryl, aralkyl, and heteroaryl;

or R^{13} comprises a 5-8 membered ring optionally containing double bonds and optionally containing one or two heteroatoms, which heteroatoms can be substituted by alkyl or acyl;

or $(R^{13})_2$ together with the heteroatom to which it is connected represents a 5-8 membered ring optionally containing double bonds and optionally containing another heteroatom, which heteroatoms can be substituted by alkyl or acyl.

A bioisostere of an acidic functional group is a functional group which has the same biological properties as an acidic functional group. One example of such a bioisostere is two neighbouring fluoro.

Heteroaryl is a 5- or 6-membered heterocyclic monocyclic group. Such a monocyclic heteroaryl group includes, for example, oxazol-2-yl, oxazol-4-yl, oxazol-5-yl, isoxazol-3-yl, isoxazol-4-yl, isoxazol-5-yl, thiazol-2-yl, thiazol-4-yl, thiazol-5-yl, isothiazol-3-yl, isothiazol-4-yl, isothiazol-5-yl, 1,2,4-oxadiazol-3-yl, 1,2,4-oxadiazol-5-yl, 1,2,4-thiadiazol-3-yl, 1,2,4-thiadiazol-5-yl, 1,2,5-oxadiazol-3-yl, 1,2,5-oxadiazol-4-yl, 1,2,5-thiadiazol-3-yl, 1,2,5-thiadiazol-4-yl, 1-imidazolyl, 2-imidazolyl, 4-imidazolyl, 1-pyrrolyl, 2-pyrrolyl, 3-pyrrolyl, 2-furanyl, 3-furanyl, 2-thienyl, 3-thienyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, 2-pyrimidinyl, 4-pyrimidinyl, 5-pyrimidinyl, 3-pyridazinyl, 4-pyridazinyl, 2-pyrazinyl, 1-pyrazolyl, 3-pyrazolyl, and 4-pyrazolyl.

A 5-8 membered ring optionally containing double bonds and optionally containing one or two heteroatoms includes for example pyrrolidine, piperidine, piperazine, morpholine, cyclohexyl, cyclohexen, dihydropyrrole, dihydrofuran, dihydrothiophen, dihydropyridine, dihydropyridazine, dihydropyrimidine, dihydropyrazine, tetrahydropyridine, tetrahydropyridazine, tetrahydropyrimidine, tetrahydropyrazine, homopiperazine, homopiperidine, azacyclooctane.

The compounds of this invention may exist in unsolvated as well as in solvated forms with pharmaceutically acceptable solvents such as water, ethanol and the like. In general, the solvated forms are considered equivalent to the unsolvated forms for the purposes of this invention.

Pharmaceutically Acceptable Salts

The chemical compound of the invention may be provided in any form suitable for the intended administration. Suitable forms include pharmaceutically (i.e. physiologically) acceptable salts, and pre- or prodrug forms of the chemical compound of the invention.

Examples of pharmaceutically acceptable addition salts include, without limitation, the non-toxic inorganic and organic acid addition salts such as the hydrochloride derived from hydrochloric acid, the hydrobromide derived from hydrobromic acid, the nitrate derived from nitric acid, the perchlorate derived from perchloric acid, the phosphate derived from phosphoric acid, the sulphate derived from sulphuric acid, the formate derived from formic acid, the acetate derived from acetic acid, the aconate derived from aconitic acid, the ascorbate derived from ascorbic acid, the benzenesulphonate derived from benzensulphonic acid, the benzoate derived from benzoic acid, the cinnamate derived from cinnamic acid, the citrate derived from citric acid, the embonate derived from embonic acid, the enantate derived from enanthic acid, the fumarate derived from fumaric acid, the glutamate derived from glutamic acid, the glycolate derived from glycolic acid, the lactate derived from lactic acid, the maleate derived from maleic acid, the malonate derived from malonic acid, the mandelate derived from mandelic acid, the methanesulphonate derived from methane

sulphonic acid, the naphthalene-2-sulphonate derived from naphtalene-2-sulphonic acid, the phthalate derived from phthalic acid, the salicylate derived from salicylic acid, the sorbate derived from sorbic acid, the stearate derived from stearic acid, the succinate derived from succinic acid, the tartrate derived from tartaric acid, the toluene-p-sulphonate derived from p-toluene sulphonic acid, and the like. Such salts may be formed by procedures well known and described in the art.

Other acids such as oxalic acid, which may not be considered pharmaceutically acceptable, may be useful in the preparation of salts useful as intermediates in obtaining a chemical compound of the invention and its pharmaceutically acceptable acid addition salt.

Metal salts of a chemical compound of the invention includes alkali metal salts, such as the sodium salt of a chemical compound of the invention containing a carboxy group.In the context of this invention the "onium salts" of N-containing compounds are also contemplated as pharmaceutically acceptable salts. Preferred "onium salts" include the alkyl-onium salts, the cycloalkyl-onium salts, and the cycloalkylalkyl-onium salts.

Prodrugs

The substance used according to the invention may be administered as such or in the form of a suitable prodrug thereof. The term "prodrug" denotes a bioreversible derivative of the drug, the bioreversible derivative being therapeutically substantially inactive per se but being able to convert in the body to the active substance by an enzymatic or non-enzymatic process.

Thus, examples of suitable prodrugs of the substances used according to the invention include compounds obtained by suitable bioreversible derivatization of one or more reactive or derivatizable groups of the parent substance to result in a bioreversible derivative. The derivatization may be performed to obtain a higher bioavailability of the active substance, to stabilize an otherwise unstable active substance, to increase the lipophilicity of the substance administered, etc.

Examples of types of substances which may advantageously be administered in the form of prodrugs are carboxylic acids, other acidic groups and amines, which may be rendered more lipophilic by suitable bioreversible derivatization. As examples of suitable groups may be mentioned bioreversible esters or bioreversible amides. Amino acids are typical examples of substances which, in their unmodified form, may have a low absorption upon administration. Suitable prodrug derivatives of amino acids will be one or both of the above-mentioned types of bioreversible derivatives.

Steric Isomers

The chemical compounds of the present invention may exist in (+) and (-) forms as well as in racemic forms. The racemates of these isomers and the individual isomers themselves are within the scope of the present invention.

Racemic forms can be resolved into the optical antipodes by known methods and techniques. One way of separating the diastereomeric salts is by use of an optically active acid, and liberating the optically active amine compound by treatment with a base. Another method for resolving racemates into the optical antipodes is based upon chromatography on an optical active matrix. Racemic compounds of the present invention can thus be resolved into their optical antipodes, e.g., by fractional crystallisation of d- or l- (tartrates, mandelates, or camphorsulphonate) salts for example.

The chemical compounds of the present invention may also be resolved by the formation of diastereomeric amides by reaction of the chemical compounds of the present invention with an optically active activated carboxylic acid such as that derived from (+) or (-) phenylalanine, (+) or (-) phenylglycine, (+) or (-) camphanic acid or by the formation of diastereomeric carbamates by reaction of the chemical compound of the present invention with an optically active chloroformate or the like.

Additional methods for the resolving the optical isomers are known in the art. Such methods include those described by *Jaques J, Collet A, & Wilen S* in "Enantiomers, Racemates, and Resolutions", John Wiley and Sons, New York (1981).

Optical active compounds can also be prepared from optical active starting materials.

Pharmaceutical Compositions

In another aspect the invention provides novel pharmaceutical compositions comprising a therapeutically effective amount of the chemical compound of the invention.

While a chemical compound of the invention for use in therapy may be administered in the form of the raw chemical compound, it is preferred to introduce the active ingredient, optionally in the form of a physiologically acceptable salt, in a pharmaceutical composition together with one or more adjuvants, excipients, carriers, buffers, diluents, and/or other customary pharmaceutical auxiliaries.

In a preferred embodiment, the invention provides pharmaceutical compositions comprising the chemical compound of the invention, or a pharmaceutically acceptable salt or derivative thereof, together with one or more pharmaceutically acceptable carriers therefor, and, optionally, other therapeutic and/or prophylactic ingredients, know and used in the art. The carrier(s) must be "acceptable" in the sense of being

compatible with the other ingredients of the formulation and not harmful to the recipient thereof.

Pharmaceutical compositions of the invention may be those suitable for oral, rectal, bronchial, nasal, topical (including buccal and sub-lingual), transdermal, vaginal or parenteral (including cutaneous, subcutaneous, intramuscular, intraperitoneal, intravenous, intraarterial, intracerebral, intraocular injection or infusion) administration, or those in a form suitable for administration by inhalation or insufflation, including powders and liquid aerosol administration, or by sustained release systems. Suitable examples of sustained release systems include semipermeable matrices of solid hydrophobic polymers containing the compound of the invention, which matrices may be in form of shaped articles, e.g. films or microcapsules.

The chemical compound of the invention, together with a conventional adjuvant, carrier, or diluent, may thus be placed into the form of pharmaceutical compositions and unit dosages thereof. Such forms include solids, and in particular tablets, filled capsules, powder and pellet forms, and liquids, in particular aqueous or non-aqueous solutions, suspensions, emulsions, elixirs, and capsules filled with the same, all for oral use, suppositories for rectal administration, and sterile injectable solutions for parenteral use. Such pharmaceutical compositions and unit dosage forms thereof may comprise conventional ingredients in conventional proportions, with or without additional active compounds or principles, and such unit dosage forms may contain any suitable effective amount of the active ingredient commensurate with the intended daily dosage range to be employed.

The chemical compound of the present invention can be administered in a wide variety of oral and parenteral dosage forms. It will be obvious to those skilled in the art that the following dosage forms may comprise, as the active component, either a chemical compound of the invention or a pharmaceutically acceptable salt of a chemical compound of the invention.

For preparing pharmaceutical compositions from a chemical compound of the present invention, pharmaceutically acceptable carriers can be either solid or liquid. Solid form preparations include powders, tablets, pills, capsules, cachets, suppositories, and dispersible granules. A solid carrier can be one or more substances which may also act as diluents, flavouring agents, solubilizers, lubricants, suspending agents, binders, preservatives, tablet disintegrating agents, or an encapsulating material.

In powders, the carrier is a finely divided solid, which is in a mixture with the finely divided active component.

In tablets, the active component is mixed with the carrier having the necessary binding capacity in suitable proportions and compacted in the shape and size desired.

The powders and tablets preferably contain from five or ten to about seventy percent of the active compound. Suitable carriers are magnesium carbonate, magnesium stearate, talc, sugar, lactose, pectin, dextrin, starch, gelatin, tragacanth, methylcellulose, sodium carboxymethylcellulose, a low melting wax, cocoa butter, and the like. The term "preparation" is intended to include the formulation of the active compound with encapsulating material as carrier providing a capsule in which the active component, with or without carriers, is surrounded by a carrier, which is thus in association with it. Similarly, cachets and lozenges are included. Tablets, powders, capsules, pills, cachets, and lozenges can be used as solid forms suitable for oral administration.

For preparing suppositories, a low melting wax, such as a mixture of fatty acid glyceride or cocoa butter, is first melted and the active component is dispersed homogeneously therein, as by stirring. The molten homogenous mixture is then poured into convenient sized moulds, allowed to cool, and thereby to solidify.

Compositions suitable for vaginal administration may be presented as pessaries, tampons, creams, gels, pastes, foams or sprays containing in addition to the active ingredient such carriers as are known in the art to be appropriate.

Liquid preparations include solutions, suspensions, and emulsions, for example, water or water-propylene glycol solutions. For example, parenteral injection liquid preparations can be formulated as solutions in aqueous polyethylene glycol solution.

The chemical compound according to the present invention may thus be formulated for parenteral administration (e.g. by injection, for example bolus injection or continuous infusion) and may be presented in unit dose form in ampoules, pre-filled syringes, small volume infusion or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulation agents such as suspending, stabilising and/or dispersing agents. Alternatively, the active ingredient may be in powder form, obtained by aseptic isolation of sterile solid or by lyophilization from solution, for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

Aqueous solutions suitable for oral use can be prepared by dissolving the active component in water and adding suitable colorants, flavours, stabilising and thickening agents, as desired.

Aqueous suspensions suitable for oral use can be made by dispersing the finely divided active component in water with viscous material, such as natural or synthetic gums, resins, methylcellulose, sodium carboxymethylcellulose, or other well known suspending agents.

Also included are solid form preparations, intended for conversion shortly before use to liquid form preparations for oral administration. Such liquid forms include solutions, suspensions, and emulsions. In addition to the active component such preparations may comprise colorants, flavours, stabilisers, buffers, artificial and natural sweeteners, dispersants, thickeners, solubilizing agents, and the like.

For topical administration to the epidermis the chemical compound of the invention may be formulated as ointments, creams or lotions, or as a transdermal patch. Ointments and creams may, for example, be formulated with an aqueous or oily base with the addition of suitable thickening and/or gelling agents. Lotions may be formulated with an aqueous or oily base and will in general also contain one or more emulsifying agents, stabilising agents, dispersing agents, suspending agents, thickening agents, or colouring agents.

Compositions suitable for topical administration in the mouth include lozenges comprising the active agent in a flavoured base, usually sucrose and acacia or tragacanth; pastilles comprising the active ingredient in an inert base such as gelatin and glycerine or sucrose and acacia; and mouthwashes comprising the active ingredient in a suitable liquid carrier.

Solutions or suspensions are applied directly to the nasal cavity by conventional means, for example with a dropper, pipette or spray. The compositions may be provided in single or multi-dose form.

Administration to the respiratory tract may also be achieved by means of an aerosol formulation in which the active ingredient is provided in a pressurised pack with a suitable propellant such as a chlorofluorocarbon (CFC) for example dichlorodifluoromethane, trichlorofluoromethane, or dichlorotetrafluoroethane, carbon dioxide, or other suitable gas. The aerosol may conveniently also contain a surfactant such as lecithin. The dose of drug may be controlled by provision of a metered valve.

Alternatively the active ingredients may be provided in the form of a dry powder, for example a powder mix of the compound in a suitable powder base such as lactose, starch, starch derivatives such as hydroxypropylmethyl cellulose and polyvinylpyrrolidone (PVP). Conveniently the powder carrier will form a gel in the nasal cavity. The powder composition may be presented in unit dose form for example in capsules or cartridges of, e.g., gelatin, or blister packs from which the powder may be administered by means of an inhaler.

In compositions intended for administration to the respiratory tract, including intranasal compositions, the compound will generally have a small particle size for example of the order of 5 microns or less. Such a particle size may be obtained by means known in the art, for example by micronization.

When desired, compositions adapted to give sustained release of the active ingredient may be employed.

The pharmaceutical preparations are preferably in unit dosage forms. In such form, the preparation is subdivided into unit doses containing appropriate quantities of the active component. The unit dosage form can be a packaged preparation, the package containing discrete quantities of preparation, such as packaged tablets, capsules, and powders in vials or ampoules. Also, the unit dosage form can be a capsule, tablet, cachet, or lozenge itself, or it can be the appropriate number of any of these in packaged form.

Tablets or capsules for oral administration and liquids for intravenous administration and continuous infusion are preferred compositions.

Further details on techniques for formulation and administration may be found in the latest edition of Remington's Pharmaceutical Sciences (Maack Publishing Co., Easton, PA).A therapeutically effective dose refers to that amount of active ingredient, which ameliorates the symptoms or condition. Therapeutic efficacy and toxicity, e.g. ED_{50} and LD_{50}, may be determined by standard pharmacological procedures in cell cultures or experimental animals. The dose ratio between therapeutic and toxic effects is the therapeutic index and may be expressed by the ratio LD_{50}/ED_{50}. Pharmaceutical compositions exhibiting large therapeutic indexes are preferred.

The dose administered must of course be carefully adjusted to the age, weight and condition of the individual being treated, as well as the route of administration, dosage form and regimen, and the result desired, and the exact dosage should of course be determined by the practitioner.

The actual dosage depend on the nature and severity of the disease being treated and the route of administration, and is within the discretion of the physician, and may be varied by titration of the dosage to the particular circumstances of this invention to produce the desired therapeutic effect. However, it is presently contemplated that pharmaceutical compositions containing of from about 0.01 to about 500 mg of active ingredient per individual dose, preferably of from about 0.1 to about 100 mg, most preferred of from about 1 to about 10 mg, are suitable for therapeutic treatments.

The active ingredient may be administered in one or several doses per day. A satisfactory result can, in certain instances, be obtained at a dosage as low as 0.01 µg/kg i.v. and 0.1 µg/kg p.o. The upper limit of the dosage range is presently considered to be about 10 mg/kg i.v. and 100 mg/kg p.o. Preferred ranges are from about 0.1 µg/kg to about 10 mg/kg/day i.v., and from about 1 µg/kg to about 100 mg/kg/day p.o.

The following examples will illustrate the invention further, however, they are not to be construed as limiting.

EXAMPLES

Example 1

In vitro blocking activity - endogenous erythrocytes chloride channels

The ability of the compounds to block the erythrocyte chloride channels cannot be demonstrated by classical electrophysiological measurements such as patch clamping, since the channel unit conductance is below the detection limit of these techniques.

All dose-response experiments were therefore performed by concomitant measurements of conductive netfluxes of chloride (J_{Cl}) and membrane potentials (V_m) in suspensions of erythrocytes (Bennekou, P. and Christophersen, P. (1986), Flux ratio of Valinomycin - Mediated K^+ Fluxes across the Human Red Cell Membrane in the presence of the Protronophore CCCP. J. Membrane Biol. 93, 221-227).

The membrane chloride conductances (G_{Cl}) were calculated by the following equation (Hodgkin, A. L. and Huxley, A.F. (1952), The components of membrane conductance in the giant axon of Loligo. J. Physiol. Lond. 116, 449-472):

$$G_{Cl} = \frac{F * J_{Cl}}{(V_m - E_{Cl})}$$

where F is the Faraday constant, E_{Cl} is the Nernst potential for the Cl-ion.

To calculate IC_{50} values (the concentration (μM) of the test substance which blocks the chloride conductance by 50%) the experimentally determined values for the normalized chloride conductance were fitted to a standard Hill type equation.

Example 2

In vitro blocking activity - malaraia parasite anion channels

The principle: The endogenous erythrocyte chloride conductance is irreversibly blocked by DIDS (4,4'-Diisothiocyanatostilbene-2,2'-disulfonic acid), whereas the malaria parasite inserted chloride channels are relatively DIDS-insensitive.

Consequently, the erythrocyte chloride conductance is irreversibly inhibited by DIDS pre-incubation and the residual chloride conductance is due to the inserted malaria parasite anion channels.

Cell preparation: Human erythrocytes are infected with malaria parasites (parasitamia > 90%). The malaria parasite infected cells are suspended in a buffer-free salt solution at a hematocrit of 20% and centrifuged for 10 min at 4000 g. The supernatant is removed and the cells are washed 2 times more following the same procedure. Packed cells are resuspended in a potassium equilibrium salt solution (66

mM NaCl, 90 mM KCl, 50 µM EGTA) containing 10 µM DIDS at a hematocrit of 10% and incubated at 37°C for ½ h. The erythrocyte suspension is transferred to centrifuge vials and washed 3 times according to the above-mentioned procedure. After the last wash the packed cells are stored on ice until use.

Method: The ability of the compounds to block the chloride conductance of the malaria parasite anion channels are measured using the above treated cells in the method as described in Example 1.

Example 3

Diagnosis of the severity of malaria disease of a human

A blood sample of a human is taken and the erythrocytes are isolated according to standard methods. Hereafter, the erythrocytes are treated as described in Example 2, to block the endogenous erythrocyte chloride conductance.

Then a sample of treated erythrocytes is tested for chloride conductance according to the method of Example 1 (without adding a ion channel blocker).

The degree of chloride conductance is a measure for how affected the human erythrocytes are by the malaria disease (the degree of parasitamia).

Example 4

Synthesis of *N*-3-Bromophenyl-*N'*-2,3-difluorophenyl urea

Under a nitrogen atmosphere was 0.5 g of 3-bromophenyl isocyanate, 0.33 g of 2,3-difluoroaniline and 0.35 mL triethylamine stirred in 25 mL of toluene (anhydrous) overnight.

The reaction mixture was evaporated to dryness. The residue was added 25 mL of water, 4M hydrochloric acid was added until pH=1, a solid precipitated and was isolated by filtration, the solid was dissolved in ethyl alcohol (96%), the mixture was heated until a clear solution was reached, 4M hydrochloric acid was added until pH=1, the solution was cooled and the product precipitated, this was isolated by filtration and dried by sucking air through it on the filter. Yield 0.58 g (70%), MP. 210-220°C.

The following compounds were prepared analogously:

N-2,3-Difluorophenyl-*N'*-3-trifluoromethylphenyl urea. (MP. 166.1-167.2°C.)

N-(4-Chloro-3-trifluoromethylphenyl)-*N'*-2,3-difluorophenyl urea. (MP.183.8-184.9°C.)

N-3,4-Dichlorophenyl-*N'*-2,3-difluorophenyl urea. (MP. 216-218°C.)

N-2,3-Difluorophenyl-*N'*-2-fluorophenyl urea. (MP. 209-210°C.)

Example 5

Synthesis of *N*-2,3-Difluorophenyl-*N'*-3-trifluoromethylphenyl thiourea

Under a nitrogen atmosphere was 0.32 g of 2,3-difluoroaniline, 0.51 g of 2-trifluoromethylphenyl thioisocyanate and 0.35 mL of triethylamine stirred in 20 mL toluene (anhydrous) overnight.

The reaction mixture was evaporated to an oil, this was trituated in water to a solid, the product was isolated by filtration and dried by sucking air through it on the filter. Yield 0.37 g (45%), MP. 88.6-90.4°C.

CLAIMS:

1. The use of a malaria parasite anion channel blocker or a pharmaceutically acceptable salt or a prodrug thereof for the manufacture of a medicament for the treatment, prevention or alleviation of malaria in a subject.

2. The use of a specific malaria parasite anion channel blocker or a pharmaceutically acceptable salt or a prodrug thereof for the manufacture of a medicament for the treatment, prevention or alleviation of malaria in a subject.

3. The use of a compound of the general formula I

$$A\text{-}(X)_p\text{-}(Y)_q\text{-}(Z)_r\text{-}B \quad (I)$$

wherein
A represents a first ring structure selected from aryl or heteroaryl;
which first ring structure is optionally substituted with one or more substituents independently selected from the group consisting of:
halogen, hydroxy, amino, oxy, cyano, nitro, trifluoromethyl, trifluoromethoxy, trifluorothiomethoxy
alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, alkoxy,
aryl, arylalkyl, aryloxy, arylcarboxy, heteroaryl, -N(R^2)-aryl,
a 5- or 6-membered monocyclic heterocyclic group,
-CO_2R^1, -COR^1, -alkyl-CO_2R^1, -alkyl-COR^1,
-$N(R^2)_2$, -alkyl-$N(R^2)_2$, -$CO_2N(R^1)_2$, -$NHCOR^1$, -$CON(R^1)_2$, -$NHSO_2R^1$,
-$CONHSO_2R^1$, -$SO_2N(R^1)_2$, and -SO_2OR^1;
wherein each of the alkyl, alkoxy, and cycloalkyl is optionally substituted with one or more substitutents independently selected from the group consisting of:
halogen, hydroxy, amino, cyano, nitro, trifluoromethyl, trifluoromethoxy, trifluorothiomethoxy alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, and alkynyl;
each of the aryl, heteroaryl, and 5- or 6-membered monocyclic heterocyclic group is optionally substituted with one or more one or more substitutents independently selected from the group consisting of:
halogen, hydroxy, amino, cyano, nitro, trifluoromethyl, trifluoromethoxy, trifluorothiomethoxy alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, alkoxy,
aryl, heteroaryl, -CO_2R^3, -COR^3,

$-N(R^4)_2$, -alkyl-$N(R^4)_2$, $-CON(R^3)_2$, $-NHCOR^3$, $-CON(R^3)_2$, $-NHSO_2R^3$, $-SO_2N(R^3)_2$, and $-SO_2OR^3$;

each of R^1 and R^3 independently is selected from the group consisting of:

hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroaryl, and

a 5-8 membered ring optionally containing double bonds and optionally containing one or two heteroatoms, which heteroatoms can be substituted with alkyl or acyl;

or $(R^1)_2$ or $(R^3)_2$ independently together with the heteroatom to which it is connected represents a 5-8 membered ring optionally containing double bonds and optionally containing another heteroatom, which heteroatom can be substituted with alkyl or acyl;

each of R^2 and R^4 independently is hydrogen or alkyl;

B represents a second ring structure selected from aryl or heteroaryl;

which second ring structure is substituted with one or more acidic functional group having a pKa value below 8, or a group which is convertible in vivo to such a group, or a bioisostere thereof;

and which second ring structure is furthermore optionally substituted with one or more substituents independently selected from the group consisting of:

halogen, hydroxy, amino, oxy, cyano, nitro, trifluoromethyl, trifluoromethoxy, trifluorothiomethoxy

alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, alkoxy,

aryl, arylalkyl, aryloxy, arylcarboxy, heteroaryl, $-N(R^6)$-aryl,

a 5- or 6-membered monocyclic heterocyclic group,

$-CO_2R^5$, $-COR^5$, -alkyl-CO_2R^5, -alkyl-COR^5,

$-N(R^6)_2$, -alkyl-$N(R^6)_2$, $-CON(R^5)_2$, $-NHCOR^5$, $-CON(R^5)_2$, $-NHSO_2R^5$, $-CONHSO_2R^5$, $-SO_2N(R^5)_2$, and $-SO_2OR^5$;

wherein each of the alkyl, alkoxy, and cycloalkyl is optionally substituted with one or more substitutents independently selected from the group consisting of:

halogen, hydroxy, amino, cyano, nitro, trifluoromethyl, trifluoromethoxy, trifluorothiomethoxy alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, and alkynyl;

each of the aryl, heteroaryl, and 5- or 6-membered monocyclic heterocyclic group is optionally substituted with one or more one or more substitutents independently selected from the group consisting of:

halogen, hydroxy, amino, cyano, nitro, trifluoromethyl, trifluoromethoxy, trifluorothiomethoxy alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, alkoxy,

aryl, heteroaryl, $-CO_2R^7$, $-COR^7$,

$-N(R^8)_2$, -alkyl-$N(R^8)_2$, $-CO_2N(R^7)_2$, $-NHCOR^7$, $-CON(R^7)_2$, $-NHSO_2R^7$, $-SO_2N(R^7)_2$, and $-SO_2OR^7$;

each of R^5 and R^7 independently is selected from the group consisting of:

hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, aryl, arylalkyl, heteroaryl, and

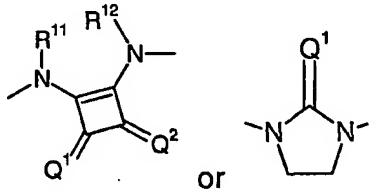
a 5-8 membered ring optionally containing double bonds and optionally containing one or two heteroatoms, which heteroatoms can be substituted by alkyl or acyl;

or $(R^5)_2$ or $(R^7)_2$ independently together with the heteroatom to which it is connected represents a 5-8 membered ring optionally containing double bonds and optionally containing another heteroatom, which heteroatom can be substituted by alkyl or acyl;

each of R^6 and R^8 independently is hydrogen or alkyl;

X, Y, and Z are independently selected from the group consisting of:
-CO-, -CS-, $-SO_2-$, $-C(=NR^9)-$, $-NR^{10}-$, $-(CH_2)_s-$, -O-,
$-CH_2-NH-$, $-SO_2-NH-$, -CH=CH-, -C≡C-, and -N=CH-;
wherein s is 1, 2, or 3;
R^9 is hydrogen, alkyl, or cyano;
R^{10} is hydrogen or alkyl;
p, q, and r independently are 0 or 1;
the sum p+q+r is 1, 2, or 3;

or $-(X)_p-(Y)_q-(Z)_r-$ represents



or

wherein
Q^1 and Q^2 independently represent O or S;
R^{11} and R^{12} independently are hydrogen or alkyl;

or a pharmaceutically acceptable salt or a prodrug thereof
for the manufacture of a medicament for the treatment, prevention or alleviation of malaria in a subject.

4. The use according to claim 3, wherein the acidic functional group having a pKa below 8, or a group which is convertible in vivo to such a group is selected from the group consisting of:

-COOH, $-CH_2CO_2R^{13}$, $-CON(R^{13})_2$, tetrazolyl, methyltetrazolyl, 3-oxo-1,2-dihydro-1,2,4-triazolyl, 2-oxo-3H-1,3,4-oxadiazolyl, 3-oxo-1,2-dihydro-1,2,4-triazolyl, 4-hydro-1,2,4-triazolyl, $-NHSO_2R^{13}$, $-CO_2R^{13}$, $-CO_2N(R^{13})_2$, $-SO_2OR^{13}$, $-SO_2N(R^{13})_2$, -CONHOH, $-CONHNH_2$, $-CONHSO_2R^{13}$, $-CONHSO_2OR^{13}$, $-PO(OR^{13})_2$, and $-SO_2OR^{13}$;

wherein each of R^{13} independently is selected from the group consisting of:

hydrogen, alkyl, cycloalkyl, cycloalkylalkyl, alkenyl, alkynyl, aryl, aralkyl, and heteroaryl;

or R^{13} comprises a 5-8 membered ring optionally containing double bonds and optionally containing one or two heteroatoms, which heteroatoms can be substituted by alkyl or acyl;

or $(R^{13})_2$ together with the heteroatom to which it is connected represents a 5-8 membered ring optionally containing double bonds and optionally containing another heteroatom, which heteroatoms can be substituted by alkyl or acyl;

and the bioisostere thereof is two neighbouring fluoro.

5. The use according to claims 3 or 4, wherein the first ring structure is optionally substituted with one or more substituents independently selected from the group consisting of:

trifluoromethyl, halogen, alkyl, alkoxy, nitro, $-COR^1$, -COOH, $-CH_2CO_2R^1$, $-CON(R^1)_2$, $-NHSO_2R^1$, $-NHCOR^1$, $-CO_2R^1$, $-CO_2N(R^1)_2$, $-SO_2N(R^1)_2$, $-CONHSO_2R^1$, $-SO_2OR^1$, and aryl;

wherein the aryl optionally is substituted with one or more substituents selected from the group:

$-NO_2$, $-NHCOR^3$, $-CO_2R^3$, $-CON(R^3)_2$, $-NHSO_2R^3$, and $-SO_2N(R^3)_2$;

wherein R^1 and R^3 are defined as above.

6. The use according to any one of the claims 3-5 wherein the second ring structure is substituted with one or more acidic functional group having a pKa value below 8, or a group which is convertible in vivo to such a group, or a bioisostere thereof;

and which second ring structure is furthermore optionally substituted with one or more substituents independently selected from the group consisting of:

alkyl, nitro, amino, alkylamino, CO_2R^9, CF_3, alkyl, halogen, hydroxy, alkoxy, $-NHCOR^5$, $-N(R^5)_2$, $-CON(R^5)_2$, and aryl,

wherein the aryl is optionally substituted with one or more substituents independently selected from the group concisting of:
$-NO_2$, $-CON(R^7)_2$, $-NHCOR^7$, $-SO_2N(R^7)_2$, and $-CO_2R^7$;
wherein R^5 and R^7 are defined as above.

7. The use according to any one of the claims 3-6, wherein the first ring structure is phenyl;
the second ring structure is phenyl; and
$-(X)_p-(Y)_q-(Z)_r-$ represents -NH-CO-NH-.

8. The use according to any one of the claims 1-7, wherein the compound of general formula I is selected from:
N-3-Trifluoromethylphenyl-*N'*-2-carboxyphenyl urea
N-3-Trifluoromethylphenyl-*N'*-3-carboxyphenyl urea;
N-(2-Methoxy-5-chlorophenyl)-*N'*-3-carboxyphenyl urea;
N-3-Trifluoromethylphenyl-*N'*-(2-carboxy-5-nitrophenyl) urea;
N-3-Trifluoromethylphenyl-*N'*-(2-carboxy-4-methylphenyl) urea;
N-3-Trifluoromethylphenyl-*N'*-(4-bromo-2-carboxyphenyl) urea;
N-3-Trifluoromethylphenyl-*N'*-3-carbamoylphenyl urea;
N-3-Trifluoromethylphenyl-*N'*-3-sulfamoylphenyl urea;
N-3-Trifluoromethylphenyl-*N'*-(5-chloro-2-phenylsulfonamidocarbonylphenyl) urea;
N-3-Trifluoromethylphenyl-*N'*-2-methylsulfonamidocarbonylphenyl urea;
N-3-Trifluoromethylphenyl-*N'*-(6-methyl-2-carboxyphenyl) urea;
N-3-Trifluoromethylphenyl-*N'*-(3-methyl-2-carboxyphenyl) urea;
N-3-Trifluoromethylphenyl-*N'*-(4-hydroxy-2-carboxyphenyl) urea;
N-4-Nitrophenyl-*N'*-2-carboxyphenyl urea;
N-3-Trifluoromethylphenyl-*N'*-2-carboxymethylphenyl urea;
N-3-Trifluoromethylphenyl-*N'*-2-sulfophenyl urea;
N-3-Trifluoromethylphenyl-*N'*-2-carboxyphenyl thiourea;
N-3-Trifluoromethylphenyl-*N'*-(2-carboxy-5-trifluoromethylphenyl) urea;
N-3-Trifluoromethylphenyl-*N'*-(4,5-dimethoxy-2-carboxyphenyl) urea;
N-3-carboxyphenyl-*N'*-(2-hydroxy-5-chlorophenyl) urea;
N-3-carbamoylphenyl-*N'*-(2-hydroxy-5-chlorophenyl) urea;
N-3-Trifluoromethylphenyl-*N'*-(2-hydroxy-4-nitro-5-carboxyphenyl) urea;
N-3-Trifluoromethylphenyl-*N'*-(4-carboxy-5-chloro-2-hydroxyphenyl) urea;
N-3-Trifluoromethylphenyl-*N'*-(2-amino-5-chlorophenyl) urea;
N-3-Trifluoromethylphenyl-*N'*-(5-chloro -2-methanesulfonylaminophenyl) urea;
N-3-Trifluoromethylphenyl-*N'*-2-carboxyphenyl urea isopropyl ester;
N-3-Trifluoromethylphenyl-*N'*-2-carboxyphenyl urea methyl ester;

N-3-Trifluoromethylphenyl-*N'*-2-hydrazinocarbonylphenyl urea;
N-3-Trifluoromethylphenyl-*N'*-2-hydroxylaminocarbonylphenyl urea;
2-(3'-Trifluoromethylbenzylcarboxamido)benzoic acid;
N-3-Trifluoromethylphenyl-*N'*-4-carboxyphenyl urea;
N-3-Trifluoromethylphenyl-*N'*-(2-carboxy-4-nitrophenyl) urea;
N-3-Trifluoromethylphenyl-*N'*-2-carboxynapht-3-yl urea;
N-3-Trifluoromethylphenyl-*N'*-(4-methoxy-2-carboxyphenyl) urea;
N-3-Methoxyphenyl-*N'*-2-carboxyphenyl urea;
N-4-Bromophenyl-*N'*-2-carboxyphenyl urea;
N-3-Nitrophenyl-*N'*-2-carboxyphenyl urea;
N-2-Methoxyphenyl-*N'*-2-carboxyphenyl urea;
N-4-Methoxyphenyl-*N'*-2-carboxyphenyl urea;
N-1-Naphthyl-*N'*-2-carboxyphenyl urea;
N-2-Trifluoromethylphenyl-*N'*-2-carboxyphenyl urea;
N-4-Methylphenylsulfonyl-*N'*-2-carboxyphenyl urea;
N-3-Trifluoromethylphenyl-*N'*-(2-ethyloxycarbonylphenyl)-1,2-diaminoethane;
N-3-Trifluoromethylphenyl-*N'*-2-carboxyphenyl sulfamide;
N-3-Trifluoromethylbenzyl-*N'*-2-carboxyphenyl urea;
N-3-(Trifluoromethyl-4-phenylphenyl)-*N'*-2-carboxyphenyl urea;
2-(3'-Trifluoromethylphenyloxycarbonylamino)benzoic acid;
N-3-Trifluoromethylphenyl-*N'*-(5-chloro-2-aminophenyl) urea;
N-3-Trifluoromethylphenyl-*N'*-(4-nitro-2-(1-*H*-tetrazol-5-yl)phenyl) urea;
N-3-Trifluoromethylphenyl-*N'*-[4-(2-naphthyl)-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-3-Trifluoromethylphenyl-*N'*-[4-(3-pyridyl)-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-3-Trifluoromethylphenyl-*N'*-[4-(1-naphthyl)-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-3-Trifluoromethylphenyl-*N'*-[4-(4-trifluoromethylphenyl)-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-3-Trifluoromethylphenyl-*N'*-[4-(3-furyl)-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-3-Trifluoromethylphenyl-*N'*-[4-(3-thienyl)-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-3-Trifluoromethylphenyl-*N'*-[4-(3-nitrophenyl)-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-3-Trifluoromethylphenyl-*N'*-[4-(4-ethoxycarbonylphenyl)-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-3-Trifluoromethylphenyl-*N'*-[4-(4-dimethylaminocarbonylphenyl)-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-3-Trifluoromethylphenyl-*N'*-[4-(4-aminocarbonylphenyl)-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-3-Trifluoromethylphenyl-*N'*-2-(4-hydroxy-1,2,4-triazol-3-yl)phenyl urea;
N-3-Trifluoromethylphenyl-*N'*-2-(3-oxo-1,2-dihydro-1,2,4-triazol-1-yl)phenyl urea;
N-3-Trifluoromethylphenyl-*N'*-2-(2-oxo-3H-1,3,4-oxadiazol-5-yl)phenyl urea;

N-3-Trifluoromethylphenyl-*N'*-[5-phenyl-2-(3-oxo-1,2-dihydro-1,2,4-triazol-1-yl)phenyl] urea;
N-3-Trifluoromethylphenyl-*N'*-[4-amino-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-3-Trifluoromethylphenyl-*N'*-[4-acetylamino-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-3-Trifluoromethylphenyl-*N'*-[4-benzoylamino-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-3-Trifluoromethylphenyl-*N'*-[4-(4-carboxyphenyl)-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-3-Trifluoromethylphenyl-*N'*-[4-(4-anilinocarbonylphenyl)-2-(1-*H*-tetrazol-5-yl)]phenyl urea;
N-4-Biphenylyl-*N'*-2-(1-*H*-tetrazol-5-yl)phenyl urea;
N-3-Biphenylyl-*N'*-2-(1-*H*-tetrazol-5-yl)phenyl urea;
N-5-Indanyl-*N'*-2-(1-*H*-tetrazol-5-yl)phenyl urea;
N-3-Bromophenyl-*N'*-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-3-Acetylphenyl-*N'*-2-(1-*H*-tetrazol-5-yl)phenyl urea;
N-3-Biphenylyl-*N'*-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-3-(3-Pyridyl)phenyl-*N'*-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-3-Trifluoromethylphenyl-*N'*-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-3-Trifluoromethylphenyl-*N'*-[2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-3-Trifluoromethylphenyl-*N'*-2-(1-*H*-tetrazol-5-yl)phenyl thiourea;
N-3-Trifluoromethylphenyl-*N'*-[4-phenyl-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-4-Trifluoromethylphenyl-*N'*-2-(1-*H*-tetrazol-5-yl)phenyl urea;
N-3-Chlorophenyl-*N'*-2-(1-*H*-tetrazol-5-yl)phenyl urea;
N-Phenyl-*N'*-2-(1-*H*-tetrazol-5-yl)phenyl urea;
N-3-Bromophenyl-*N'*-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
3-[4-Bromo-2-(1-*H*-tetrazol-5-yl)-phenylamino]-4-(3-trifluoromethyl-phenylamino)-3-cyclobuten-1,2-dione;
3-(3-Bromo-phenylamino)-4-[4-bromo-(1-*H*-tetrazol-5-yl)-phenylamino]-3-cyclobuten-1,2-dione;
3-(3-Bromo-phenylamino)-4-[4´-(N,N-dimethyl sulfonamide)-2-(1-*H*-tetrazol-5-yl)-biphenylamino]-3-cyclobuten-1,2-dione;
3-(3-Bromo-phenylamino)-4-[2-(1-*H*-tetrazol-5-yl)-biphenylamino]-3-cyclobuten-1,2-dione;
N-Phenyl-*N´*-(2-carboxyphenyl) urea;
N-3-Trifluoromethylphenyl-*N´*-(2-carboxyphenyl)-*N´*-methyl urea;
N-3-Trifluoromethylphenyl-*N´*-(4-bromo-2-carboxyphenyl) urea;
N-3-Trifluoromethylphenyl-*N´*-(2-carboxy-4-chlorophenyl) urea;
N-3-Trifluoromethylphenyl-*N'*-(5-bromo-2-carboxyphenyl) urea;
N-3-Trifluoromethylphenyl-*N'*-(2-carboxy-5-chlorophenyl) urea;
N-3-Trifluoromethylphenyl-*N´*-(2-carboxy-4-fluorophenyl) urea;
N-3-Bromophenyl)-*N´*-[2-(1-*H*-tetrazol-5-yl)-4-biphenyl] urea;

N-3-Trifluoromethylphenyl)-*N*´-[4´-(N,N-dimethylsulfamoyl)-2-(1-*H*-tetrazol-5-yl)-4-biphenyl} urea;
N-3-Bromophenyl-*N*´-[4´-(N,N-dimethylsulfamoyl)-2-(1-*H*-tetrazol-5-yl)-4-biphenyl] urea;
N-3-Bromophenyl-*N*´-[4´-(N,N-dimethylcarbamoyl)-2-(1-*H*-tetrazol-5-yl)-4-biphenyl] urea;
N-3-Trifluromethylphenyl-*N*´-[4-amino-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-3-Trifluoromethylphenyl-*N*´-[4-acetylamino-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-3-Trifluoromethylphenyl-*N*´-[4´-carbamoyl-2-(1-*H*-tetrazol-5-yl)-4-biphenyl] urea;
N-3-Trifluoromethylphenyl-*N*´-[4´-(N,N-dimethylcarbamoyl)-2-(1-*H*-tetrazol-5-yl)-4-biphenyl] urea;
N-3-Trifluoromethylphenyl-*N*´-[4´-carboxy-2-(1-*H*-tetrazol-5-yl)-4-biphenyl] urea;
1-(3-Trifluoromethylphenyl)-3-(2-carboxyphenyl)-2-imidazolidone;
N-3-Trifluoromethylphenyl-*N*'-[4-(4-benzoylcarbonylphenyl)-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-4-Biphenylyl-*N*'-2-(1-*H*-tetrazol-5-yl)phenyl urea;
N-3-Bromophenyl-*N*´-[3´-nitro-2-(1-*H*-tetrazol-5-yl)biphenyl] urea;
N-3-Bromophenyl-*N*´-[4´-(sulfoamido-N-methylpiperazinium chloride)-2-(1-*H*-tetrazol-5-yl)-4-biphenyl] urea;
N-3-Bromophenyl-*N*´-[4´-(carbamoyl-N-methylpiperazine)-2-(1-*H*-tetrazol-5-yl)-4-biphenyl] urea;
N-3,5-Dichlorophenyl-*N*´-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-4-Trifluoromethylphenyl-*N*´-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-4-Bromophenyl-*N*´-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-3-Methoxyphenyl-*N*´-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-3-Chlorophenyl-*N*´-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-3-Methylphenyl-*N*´-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl urea;
N-3,4-Dichlorophenyl-*N*´-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-2-Naphthyl-*N*´-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-(4-Methyl-3-nitrophenyl)-*N*´-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-(2-Chloro-4-trifluoromethylphenyl)-*N*´-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-3,5-Di(trifluoromethyl)phenyl-*N*´-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-3,5-Dimethylphenyl-*N*´-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-4-Ethoxyophenyl-*N*´-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-4-Methoxyphenyl-*N*´-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-2-Trifluoromethylphenyl-*N*´-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-2-Bromophenyl-*N*´-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-2-Chlorophenyl-*N*´-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-2-Fluorophenyl-*N*´-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea;

N-(4-Chloro-3-trifluoromethylphenyl)-*N*´-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-3-Bromophenyl-*N*´-2,3-difluorophenyl urea;
N-2-Methylphenyl-*N*´-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-2-Ethylphenyl-*N*´-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-4-Methylphenyl-*N*´-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-2-Nitrophenyl-*N*´-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-3-Fluorophenyl-*N*´-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-4-(2-Propyl)phenyl-*N*´-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-3-Nitrophenyl-*N*´-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-3-Acetylphenyl-*N*´-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-4-Nitrophenyl-*N*´-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-3-Trifluoromethylphenyl-*N*´-2-carboxyphenyl urea;
N-Phenyl-*N*´-2-carboxyphenyl urea;
N-3-Trifluoromethylphenyl-*N*´-2-carboxyphenyl-N-methyl urea;
N-3-Trifluoromethylphenyl-*N*´-[4´-(N-phenylcarbamoyl)-2-(1-*H*-tetrazol-5-yl)-4-biphenyl] urea;
N-(2-Indan)-*N*´-2-(1-*H*-tetrazol-5-yl)phenyl urea;
N-(4-Biphenyl)-*N*´-2-(1-*H*-tetrazol-5-yl)phenyl urea;
N-(3-Biphenyl)-*N*´-2-(1-*H*-tetrazol-5-yl)phenyl urea;
N-3-Acetylphenyl-*N*´-2-(1-*H*-tetrazol-5-yl)phenyl urea;
N-3-Trifluoromethylphenyl-*N*´-[2-(1-methyltetrazol-5-yl)-4-biphenyl] urea;
N-(3-Biphenyl)-*N*´-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-3-(3-Pyridyl)phenyl-*N*´-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea hydrochloride;
N-3-Bromophenyl-*N*´-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-(4-Biphenylyl)-*N*'-2-(1-*H*-tetrazol-5-yl)phenyl urea;
N-(3-biphenylyl)-*N*'-2-(1-*H*-tetrazol-5-yl)phenyl urea;
N-(5-Indanyl)-*N*'-2-(1-*H*-tetrazol-5-yl)phenyl urea;
N-(2-Chloro-5-trifluoromethylphenyl)-N´-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea
N-4-Bromophenyl-*N*´-(2-carboxy-5-chlorophenyl) urea;
N-4-Trifluoromethylphenyl-*N*´-(2-carboxy-5-chlorophenyl) urea;
N-3-Bromophenyl-*N*´-(2-carboxy-5-chlorophenyl) urea;
N-3-Nitrophenyl-*N*´-(2-carboxy-5-chlorophenyl) urea;
N-3-Methoxyphenyl-*N*´-(2-carboxy-5-chlorophenyl) urea;
N-(4-Chloro-3-trifluoromethylphenyl)-*N*´-(2-carboxy-5-chlorophenyl) urea;
N-3-Fluorophenyl-*N*´-(2-carboxy-5-chlorophenyl) urea;
N-3-Fluorophenyl-*N*´-(2-carboxy-5-fluorophenyl) urea;
N-3-Trifluoromethylphenyl-*N*´-(2-carboxy-4,5-difluorophenyl) urea;
N-3,5-Bis(trifluoromethyl)phenyl-*N*´-(2-carboxy-5-chlorophenyl) urea;
N-3-Trifluoromethylphenyl-*N*´-(2-carboxy-5-nitrophenyl) urea;

N-3,4-Dichlorophenyl-*N'*-[5-methyl-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-3,4-Dichlorophenyl-*N'*-[5-chloro-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-3-Trifluoromethylphenyl-*N'*-(3-carboxy-4-chlorophenyl) urea;
N-(3-Chloro-4-hydroxyphenyl)-*N'*-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-2,3,4-Trifluorophenyl-*N'*-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-3,4-Difluorophenyl-*N'*-[4-bromo-2-(1-*H*-tetrazol-5yl)phenyl] urea;
N-3-Chlorophenyl-*N'*-2,3-difluorophenyl urea;
N-(3-Chloro-4-fluorophenyl)-*N'*-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-2,4,5-Trifluorophenyl-*N'*-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-3,5-Bis(trifluoromethyl)phenyl-*N'*-[2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-3,5-Bis(trifluoromethyl)phenyl-*N'*-[2,4-dibromo-6-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-(4-Fluoro-3-trifluoromethylphenyl)-*N'*-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-3,5-Difluorophenyl-*N'*-[4-bromo-2-(1-*H*-tetrazol-5-yl)-phenyl] urea;
N-3,5-Bis(trifluoromethyl)phenyl-*N'*-[4'-(*N*,*N*-dimethylsulfamoyl)-2-(1-*H*-tetrazol-5-yl)-4-biphenyl] urea;
N-3,5-Dichlorophenyl-*N'*-[4'-(*N*,*N*-dimethylsulfamoyl)-2-(1-*H*-tetrazol-5-yl)-4-biphenyl] urea;
N-2,3-Difluorophenyl-*N'*-3-trifluoromethylphenyl urea;
N-2,3-Difluorophenyl-*N'*-(4-chloro-3-trifluoromethylphenyl) urea;
N-3,4-Dichlorophenyl-*N'*-2,3-difluorophenyl;
N-2,3-Difluorophenyl-*N'*-3-trifluoromethylphenyl thiourea;
N-2,3-Difluorophenyl-*N'*-2-fluorophenyl urea;
N-2,3-Difluorophenyl-*N'*-3-methoxyphenyl urea;
N-3,4-Dichlorophenyl-*N'*-2,3,4-trifluorophenyl urea;
N-(4-Chloro-3-trifluoromethylphenyl)-*N'*-2,3,4-trifluorophenyl urea;
N-3-Chlorophenyl-*N'*-(2-hydroxy-4-methylphenyl) urea;
N-2,3-Difluorophenyl-*N'*-[3-(pyridin-3-yl)-phenyl] urea;
N-3,5-Dichlorophenyl-*N'*-2,3-difluorophenyl urea;
N-2,3-Difluorophenyl-*N'*-3-nitrophenyl urea; and
pharmaceutically acceptable salts and prodrugs thereof.

9. A method for the treatment, prevention, or alleviation of malaria in a subject comprising administering to said subject a therapeutically effective amount of a malaria parasite anion blocker
or a pharmaceutically acceptable salt or a prodrug thereof.

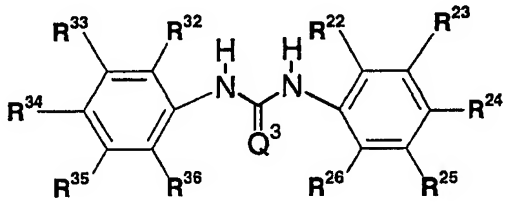
10. A method for screening a chemical compound for activity in the treatment, prevention or alleviation of malaria in a subject, which method comprises the following steps:

- subjecting a malaria anion channel containing cell to the action of the chemical compound;
- monitoring the membrane potential, and the conductive netflux of chloride of the malaria anion channel containing cell; and
- calculating the ability of the compound to block the malaria anion channel.

11. A method for diagnosing the severity of malaria disease of a subject, which method comprises the following steps:

- isolating erythrocytes of a blood sample of said subject;
- blocking the endogenous erythrocyte chloride channels of the erythrocytes;
- monitoring the membrane potential, and the conductive netflux of chloride over the erythrocyte cell membranes;
- calculating the residual chloride conductance of the erythrocyte cell membranes;
- calculating the degree of parasitamia.

12. A compound of the general formula II



II

wherein one of R^{22}, R^{23}, R^{24}, R^{25}, or R^{26} is

-COOH, -OH, or 1-H-tetrazol-5-yl; or R^{22} and R^{23} are fluoro;

or R^{23} and R^{24} are fluoro;

the other three or four of R^{22}, R^{23}, R^{24}, R^{25}, and R^{26} are independently selected from the group consisting of:

hydrogen, chloro, fluoro, nitro, methyl, bromo, and 4-(dimethylsulfamoyl)-phenyl;

R^{32}, R^{33}, R^{34}, R^{35}, and R^{36} are independently selected from the group consisting of:

hydrogen, bromo, trifluoromethyl, nitro, methoxy, chloro, fluoro, and hydroxy;

Q^3 is O or S;

or a pharmaceutically acceptable salt or a prodrug thereof.

13. A compound according to claim 12 selected from

N-(2-Chloro-5-trifluoromethylphenyl)-*N'*-[4-bromo-2-(1-H-tetrazol-5-yl)phenyl] urea;

N-4-Bromophenyl-*N'*-(2-carboxy-5-chlorophenyl) urea;

N-4-Trifluoromethylphenyl-*N'*-(2-carboxy-5-chlorophenyl) urea;

N-3-Bromophenyl-*N'*-(2-carboxy-5-chlorophenyl) urea;

N-3-nitrophenyl-*N'*-(2-carboxy-5-chlorophenyl) urea;
N-3-Methoxyphenyl-*N'*-(2-carboxy-5-chlorophenyl) urea;
N-(4-Chloro-3-trifluoromethylphenyl)-*N'*-(2-carboxy-5-chlorophenyl) urea;
N-3-Fluorophenyl-*N'*-(2-carboxy-5-chlorophenyl) urea;
N-3-fluorophenyl-*N'*-(2-carboxy-5-fluorophenyl) urea;
N-3-Trifluoromethylphenyl-*N'*-(2-carboxy-4,5-difluorophenyl) urea;
N-3,5-Bis(trifluoromethyl)phenyl)-*N'*-(2-carboxy-5-chlorophenyl) urea;
N-3-Trifluoromethylphenyl-*N'*-(2-carboxy-5-nitrophenyl) urea;
N-3,4-Dichlorophenyl-*N'*-[5-methyl-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-3,4-Dichlorophenyl-*N'*-[5-chloro-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-3-Trifluoromethylphenyl-*N'*-(3-carboxy-4-chlorophenyl) urea;
N-(3-Chloro-4-hydroxyphenyl)-*N'*-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-2,3,4-Trifluorophenyl-*N'*-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-3,4-Difluorophenyl-*N'*-[4-bromo-2-(1-*H*-tetrazol-5yl)phenyl] urea;
N-3-Chlorophenyl-*N'*-2,3-difluorophenyl urea;
N-(3-Chloro-4-fluorophenyl)-*N'*-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl) urea;
N-2,4,5-Trifluorophenyl)-*N'*-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-3,5-Bis{trifluoromethyl}phenyl)-*N'*-[2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-3,5-Bis(trifluoromethyl)phenyl-*N'*-[2,4-dibromo-6-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-(4-Fluoro-3-trifluoromethylphenyl)-*N'*-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-3,5-Difluorophenyl-*N'*-[4-bromo-2-(1-*H*-tetrazol-5-yl)phenyl] urea;
N-3,5-Bis(trifluoromethyl)phenyl-*N'*-[4'-(*N*,*N*-dimethylsulfamoyl)-2-(1-*H*-tetrazol-5-yl)-4-biphenyl] urea;
N-3,5-Dichlorophenyl-*N'*-[4'-(*N*,*N*-dimethylsulfamoyl)-2-(1-*H*-tetrazol-5-yl)-4-biphenyl] urea;
N-2,3-Difluorophenyl-*N'*-3-trifluoromethylphenyl urea;
N-2,3-Difluorophenyl-*N'*-(4-chloro-3-trifluoromethylphenyl) urea;
N-3,4-Dichlorophenyl-*N'*-2,3-difluorophenyl;
N-2,3-Difluorophenyl-*N'*-3-trifluoromethylphenyl) thiourea;
N-2,3-Difluorophenyl-*N'*-2-fluorophenyl urea;
N-2,3-Difluorophenyl-*N'*-3-methoxyphenyl) urea;
N-3,4-Dichlorophenyl-*N'*-2,3,4-trifluorophenyl urea;
N-(4-Chloro-3-trifluoromethylphenyl)-*N'*-2,3,4-trifluorophenyl urea;
N-3-Chlorophenyl-*N'*-(2-hydroxy-4-methylphenyl) urea;
N-2,3-Difluorophenyl-*N'*-[3-(pyridin-3-yl)-phenyl] urea;
N-3-Chlorophenyl-*N'*-2,3-difluorophenyl urea;
N-3,5-Dichlorophenyl-*N'*-2,3-difluorophenyl urea;
N-2,3-Difluorophenyl-*N'*-3-nitrophenyl urea; and
pharmaceutically acceptable salts and prodrugs thereof.